

? ds

Set	Items	Description
S1	28138	CAPTOPRIL
S2	256835	METASTAS?
S3	23	S1 AND S2
S4	15	RD (unique items)
S5	8	S4 AND PY<=1996

? s benign

S6 157803 BENIGN

? s s1 and s6

28138 S1
157803 S6

S7 44 S1 AND S6

? s s7 and py<=1996

Processing

44 S7
29341310 PY<=1996
S8 36 S7 AND PY<=1996

? s malignan?

S9 444482 MALIGNAN?

? s s8 and s9

36 S8
444482 S9

S10 7 S8 AND S9

? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records

S11 6 RD (unique items)

? t s11/3,k,ab/1-6

11/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

07270232 90335607 PMID: 2198982

The effect of **Captopril** on **benign** and **malignant** reactions in irradiated rat skin.

Ward WF; Molteni A; Ts'ao C; Hinz JM

Department of Radiology, Northwestern University Medical School, Chicago, IL 60611.

British journal of radiology (ENGLAND) May 1990, 63 (749)

p349-54, ISSN 0007-1285 Journal Code: B28

Contract/Grant No.: HL25106, HL, NHLBI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The effect of the angiotensin converting enzyme inhibitor **Captopril** on the severity of radiation-induced epilation and moist desquamation and the incidence of skin tumours was determined for up to 52 weeks in male rats. The irradiation consisted of a range of single doses (0, 10, 20, 30 Gy) of ⁶⁰Co gamma rays to a 3.5 cm² right hemithorax port. Half of each radiation dose group consumed control powdered chow, and half consumed chow containing **Captopril** (50 mg/kg/day) continuously after irradiation. There were time- and radiation-dose-dependent increases in all three skin

reactions. Rats exposed to 10 Gy exhibited a mild and transient epilation, but no moist desquamation or neoplasia in the radiation port. In animals exposed to 30 Gy, however, epilation began at 2 weeks after irradiation, reached a peak at approximately 7 weeks, then persisted essentially unchanged through 52 weeks. **Captopril** had no significant effect on the epilation reaction. Two waves of moist desquamation were observed after 30 Gy. The first appeared at 3 weeks after irradiation, reached a peak from 6-10 weeks, then subsided partially but significantly from 12-26 weeks. The second wave of moist desquamation began at 26-28 weeks, often was ulcerative, and occasionally was accompanied by the appearance of tumours in the irradiated volume. **Captopril** significantly (p less than 0.05) reduced the severity of both phases of the moist desquamation reaction after 30 Gy, and reduced the percentage of animals exhibiting the most severe desquamation score (involving 50% of the radiation port). Of particular interest was the observation that **Captopril** also reduced the incidence of tumours. Of the 14 tumours detected, all were **malignant** (fibrosarcomas, squamous cell carcinomas), and only three (p less than 0.05) occurred in rats receiving **Captopril**. Multiple tumours (three cases), tumours induced by 20 Gy (three cases), and tumours appearing before 6 months (one case) were observed only in rats consuming control diet, never in **Captopril**-treated animals. Animals which developed tumours in the second 6 months post-irradiation exhibited significantly more severe moist desquamation during the first 6 months than did the tumour-free members of their treatment group. Thus **Captopril**, known to ameliorate acute lung damage in irradiated rats, also reduces chronic **benign** and **malignant** skin reactions in the radiation treatment field.

The effect of **Captopril** on **benign** and **malignant** reactions in irradiated rat skin.

May 1990,

The effect of the angiotensin converting enzyme inhibitor **Captopril** on the severity of radiation-induced epilation and moist desquamation and the incidence of skin...

... Half of each radiation dose group consumed control powdered chow, and half consumed chow containing **Captopril** (50 mg/kg/day) continuously after irradiation. There were time- and radiation-dose-dependent increases ...

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... the first 6 months than did the tumour-free members of their treatment group. Thus **Captopril**, known to ameliorate acute lung damage in irradiated rats, also reduces chronic **benign** and **malignant** skin reactions in the radiation treatment field.

Descriptors: **Captopril**--therapeutic use--TU; *Radiation Injuries, Experimental--prevention and control--PC; *Skin--radiation effects--RE;

*Skin...

Chemical Name: **Captopril**

11/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

06531451 87312175 PMID: 2887673

Characterization of neurohormonal changes following the production of the **benign** and **malignant** phases of two-kidney, two-clip Goldblatt hypertension.

Suzuki H; Saruta T; Ferrario CM; Brosnihan KB

Japanese heart journal (JAPAN) May 1987, 28 (3) p413-26,

ISSN 0021-4868 Journal Code: KH3

Contract/Grant No.: HL-6835, HL, NHLBI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The neurohormonal contribution to high blood pressure was investigated in 9 conscious two-kidney, two-clip Goldblatt (2K2C) hypertensive dogs during evolution of the **benign** and **malignant** phases after application of bilateral renal clips (BRC). Serial measurements were taken of the plasma renin activity (PRA), plasma angiotensin I-immunoreactivity (Ang I-ir), plasma angiotensin II-ir (Ang II-ir), renin substrate (RS) catecholamines [epinephrine (Epi) and norepinephrine (NE)] and vasopressin (AVP). Immediately after BRC, the elevation of the blood pressure (86 +/- 3 to 110 +/- 3 mmHg, p less than 0.01) was associated with an increase in heart rate (93 +/- 3 to 114 +/- 9 beats/min, p less than 0.01). These hemodyna

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S4	15	RD (unique items)
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S6	157803	BENIGN
S7	44	S1 AND S6
S8	36	S7 AND PY<=1996
S9	444482	MALIGNAN?
S10	7	S8 AND S9
S11	6	RD (unique items)

? s sulphydryl(w)donor

36520 SULFHYDRYL

199419 DONOR

S12 64 SULFHYDRYL(W)DONOR

? s s1 and s12

28138 S1

64 S12

S13 6 S1 AND S12

? s thiorphan

S14 1564 THIORPHAN

? s s14 and s12

1564 S14

64 S12

S15 0 S14 AND S12

? t s13/3,k,aab/1-6

>>>Only one format type allowed

? t s13/3,k,ab/1-6

13/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10361008 99408399 PMID: 10480522

ACE inhibitors improve endothelial function in type 1 diabetic patients with normal arterial pressure and microalbuminuria.

Arcaro G; Zenere BM; Saggiani F; Zenti MG; Monauni T; Lechi A; Muggeo M; Bonadonna RC

Division of Internal Medicine, Azienda Ospedaliera di Verona, University of Verona School of Medicine, Italy.

Diabetes care (UNITED STATES) Sep 1999, 22 (9) p1536-42, ISSN 0149-5992 Journal Code: EAG

Languages: ENGLISH

Document type: Clinical Trial; Journal Article; Randomized Controlled Trial

Record type: Completed

OBJECTIVE: The purpose of this study was to test whether a short-course treatment with ACE inhibitors may restore endothelium-dependent and/or -independent vasodilation in the femoral artery of microalbuminuric patients with type 1 diabetes and normal arterial pressure. RESEARCH DESIGN AND METHODS: We studied nine normotensive microalbuminuric type 1 diabetic patients and two groups of control subjects matched for femoral artery diameter to type 1 diabetic patients after placebo (control group A, n = 17) and ACE inhibitor (control group B, n = 18) treatment, respectively. The patients were enrolled in a double-blind cross-over study with a 1-week

trial of either placebo, **captopril** (25 mg t.i.d.), or enalapril (10 mg/day) in randomized order to ascertain whether short-term ACE inhibition obtained with (**captopril**) or without (enalapril) a **sulphydryl donor** molecule ameliorates vessel wall function. Endothelium-mediated flow-dependent vasodilation and endothelium-independent vasodilation were evaluated in the right common femoral artery by echo Doppler. RESULTS: Both **captopril** and enalapril normalized (control group B 22.9+/-3.2% per 8 min) endothelium-dependent response (19.6+/-7.5 and 18.0+/-5.3 vs. -10.4+/-4.1% per 8 min, $P < 0.01$, for both **captopril** and enalapril versus placebo, respectively) in the type 1 diabetic patients. **Captopril** (28.4+/-3.5 vs. 17.1+/-3.5% per 5 min during placebo, $P < 0.05$) but not enalapril (20.1+/-3.0 vs. 31.7+/-2.8% per 5 min, $P < 0.05$ for enalapril versus control group B, and NS for **captopril** vs. control group B) ameliorated endothelium-independent vasodilation in type 1 diabetic patients. CONCLUSIONS: ACE inhibition improves endothelium-dependent vasodilation in the femoral artery of normotensive microalbuminuric type 1 diabetic patients. **Captopril** also ameliorates endothelium-independent vasodilation, possibly through its **sulphydryl donor** properties. These results may be of pathophysiological relevance to prevent cardiovascular complications in these patients.

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13/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

07481552 92096893 PMID: 1756422

Vasodilator therapy: interaction of nitrates with angiotensin-converting enzyme inhibitors.

Juggi JS; Koenig-Berard E; Vitou P

Institute de Recherches Internationales, Servier, Courbevoie, France.

Canadian journal of cardiology (CANADA) Nov 1991, 7 (9) p419-25,

ISSN 0828-282X Journal Code: CHP

Languages: ENGLISH

Document type: Journal Article; Review; Review, Tutorial

Record type: Completed

Nitrates and other nitrovasodilators are locally acting agents. Their efficacy is reported to depend upon the availability of sulphydryl groups in vascular smooth muscle. Long term nitrovasodilator therapy has limited effectiveness, and development of nitrate tolerance has been recognized to be due to exhaustion of the tissue sulphydryl pool, in addition to

vasodilation-induced reflex activation of the neurohumoral system. Under both experimental and clinical conditions it has been demonstrated that N-acetylcysteine and other exogenously introduced sulfhydryl donors potentiate hemodynamic responses to nitrates and reverse nitrate tolerance. The newer group of angiotensin-converting enzyme (ACE) inhibitor drugs has been reported to be effective in reducing afterload and preload in a variety of experimental and clinical trials. **Captopril**, the first developed ACE inhibitor, and its analogs contain sulfhydryl groups. Although the sulfhydryl group of **captopril** is not thought to be responsible for its vasodilator action, it can act as a **sulfhydryl donor** to promote nitrate effectiveness and prevent development of tolerance. Limited experimental and clinical trials on combined therapy with nitrates and **captopril** have produced promising results. An ingenious prototype compound, S-nitrosocaptopril, has recently been synthesized. This is an exciting new development in vasodilator therapy, but clinical application must await full experimental characterization of this and other identical compounds.

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13/3,K,AB/3 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)
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12420620 BIOSIS NO.: 200000174122
Study on the action of **captopril**: A **sulfhydryl donor** on rodent ulcer.
AUTHOR: Dau Harminder; Chauhan C K; Shahani S(a)
AUTHOR ADDRESS: (a)Department of Pharmacology, L.T.M. Medical College and L.T.M.G. Hospital Sion, Mumbai**India
JOURNAL: Indian Journal of Pharmacology. 32 (1):p25-27 Feb., 2000
ISSN: 0253-7613
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Objective: To evaluate ulcero-protective property of **captopril**-a **sulfhydryl donor** in rats. Methods: The study was done in rats by inducing gastric ulcer by oxyphenbutazone, 0.6 M hydrochloric acid and restrain stress and the effect of different doses of **captopril** alone or/and omeprazole was studied. Effect of paracetamol-a depleter of glutathione of stomach was observed over **captopril** and/or omeprazole. Results: **Captopril** produced dose dependent protection against experimentally induced gastric ulcer in rats. Its ulcero-protective effect was enhanced by omeprazole. Paracetamol reduced the protection offered by both the agents alone and in combination. Conclusion: **Captopril** produced dose dependent protection against experimentally induced gastric ulcer. Its protective effect was enhanced by omeprazole and reduced by paracetamol suggesting a possible involvement of sulfhydryl group of **captopril** in ulcer protection.

Study on the action of **captopril**: A **sulphydryl donor** on rodent ulcer.

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...REGISTRY NUMBERS: **CAPTOPRIL**;

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: **captopril**----

...antiulcer-drug, **sulphydryl donor**, ulcero-protective effect

13/3,K,AB/4 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2002 Inst for Sci Info. All rts. reserv.

07977778 Genuine Article#: 231YG Number of References: 39
Title: ACE inhibitors improve endothelial function in type 1 diabetic patients with normal arterial pressure and microalbuminuria (ABSTRACT AVAILABLE)

Author(s): Arcaro G; Zenere BM; Saggiani F; Zenti MG; Monauni T; Lechi A; Muggeo M; Bonadonna RC (REPRINT)

Corporate Source: OSPED CIVILE,DIV ENDOCRINOL & METAB DIS, PIAZZALE STEFANI 1/I-137126 VERONA//ITALY/ (REPRINT); UNIV VERONA,SCH MED, AZIENDA OSPED VERONA, DIV ENDOCRINOL & METAB DIS/I-37100 VERONA//ITALY//; UNIV VERONA,SCH MED, AZIENDA OSPED VERONA, DIV INTERNAL MED/I-37100 VERONA//ITALY/

Journal: DIABETES CARE, 1999, V22, N9 (SEP), P1536-1542

ISSN: 0149-5992 Publication date: 19990900

Publisher: AMER DIABETES ASSOC, 1660 DUKE ST, ALEXANDRIA, VA 22314

Language: English Document Type: ARTICLE

Abstract: OBJECTIVE - The purpose of this study was to test whether a short-course treatment with ACE inhibitors may restore endothelium-dependent and/or -independent vasodilation in the femoral artery of microalbuminuric patients with type 1 diabetes and normal arterial pressure.

RESEARCH DESIGN AND METHODS - We studied nine normotensive microalbuminuric type 1 diabetic patients and two groups of control subjects matched for femoral artery diameter to type I diabetic patients after placebo (control group A, n = 17) and ACE inhibitor (control group B, n = 18) treatment, respectively. The patients were enrolled in a double-blind cross-over study with a 1-week trial of either placebo, **captopril** (25 mg t.i.d.), or enalapril (10 mg/day) in randomized order to ascertain whether short-term ACE inhibition obtained with (**captopril**) or without (enalapril) a **sulphydryl donor** molecule ameliorates Vessel wall function. Endothelium-mediated Row-dependent vasodilation and endothelium-independent vasodilation were evaluated in the right common femoral artery by echo Doppler.

RESULTS - Both **captopril** and enalapril normalized (control

group B 22.9 +/- 3.2% per 8 min) endothelium-dependent response (19.6 +/- 7.5 and 18.0 +/- 5.3 vs. -10.4 +/- 4.1% per 8 min, P < 0.01, for both **captopril** and enalapril versus placebo, respectively) in the type I diabetic patients. **Captopril** (28.4 +/- 3.5 vs. 17.1 +/- 3.5%, per 5 min during placebo, P < 0.05) but not enalapril (20.1 +/- 3.0 vs. 31.7 +/- 2.8% per 5 min, P < 0.05 for enalapril Versus control group B, and NS for **captopril** vs. control group B) ameliorated endothelium-independent vasodilation in type 1 diabetic patients.

CONCLUSIONS - ACE inhibition improves endothelium-dependent vasodilation in the femoral artery of normotensive microalbuminuric type 1 diabetic patients. **Captopril** also ameliorates endothelium-independent vasodilation, possibly through its **sulphydryl donor** properties. These results may beef pathophysiological relevance to prevent cardiovascular complications in these patients.

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13/3,K,AB/5 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2002 Inst for Sci Info. All rts. reserv.

01358669 Genuine Article#: GR722 Number of References: 0
(NO REFS KEYED)

Title: VASODILATOR THERAPY - INTERACTION OF NITRATES WITH
ANGIOTENSIN-CONVERTING ENZYME-INHIBITORS (Abstract Available)

Author(s): JUGGI JS; KOENIGBERARD E; VITOU P

Corporate Source: ARABIAN GULF UNIV, COLL MED & MED SCI, POB
22979/BAHRAIN//SAUDI ARABIA/

Journal: CANADIAN JOURNAL OF CARDIOLOGY, 1991, V7, N9, P419-425

Language: ENGLISH Document Type: REVIEW

Abstract: Nitrates and other nitrovasodilators are locally acting agents. Their efficacy is reported to depend upon the availability of sulphydryl groups in vascular smooth muscle. Long term nitrovasodilator therapy has limited effectiveness, and development

of nitrate tolerance has been recognized to be due to exhaustion of the tissue sulfhydryl pool, in addition to vasodilation-induced reflex activation of the neurohumoral system. Under both experimental and clinical conditions it has been demonstrated that N-acetylcysteine and other exogenously introduced sulfhydryl donors potentiate hemodynamic responses to nitrates and reverse nitrate tolerance. The newer group of angiotensin-converting enzyme (ACE) inhibitor drugs has been reported to be effective in reducing afterload and preload in a variety of experimental and clinical trials. **Captopril**, the first developed ACE inhibitor, and its analogs contain sulfhydryl groups. Although the sulfhydryl group of **captopril** is not thought to be responsible for its vasodilator action, it can act as a **sulfhydryl donor** to promote nitrate effectiveness and prevent development of tolerance. Limited experimental and clinical trials on combined therapy with nitrates and **captopril** have produced promising results. An ingenious prototype compound, S-nitrosocaptopril, has recently been synthesized. This is an exciting new development in vasodilator therapy, but clinical application must await full experimental characterization of this and other identical compounds.

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13/3,K,AB/6 (Item 1 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent
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Dialog Acc No: 3032363 IFI Acc No: 9829817

Document Type: C

METHODS AND COMPOSITIONS FOR GENERATING ANGIOSTATIN; CONTACTING PLASMINOGEN OF PLASMIN WITH A PLASMINOGEN ACTIVATOR AND A **SULFHYDRYL DONOR**

Inventors: Gately Stephen T (US); Soff Gerald (US); Twardowski Przemyslaw (US)

Assignee: Northwestern University Assignee Code: 60920

Publication (No,Date), Applic (No,Date)

US 5801012 19980901 US 96710305 19960917

Publication Kind: A

Calculated Expiration: 20160917

Priority Applic(No,Date): US 96710305 19960917

Abstract:

The invention provides a method of generating angiotatin in vitro comprising contacting plasminogen or plasmin with a plasminogen activator and a **sulfhydryl donor**.

...CONTACTING PLASMINOGEN OF PLASMIN WITH A PLASMINOGEN ACTIVATOR AND A **SULFHYDRYL DONOR**

Abstract:

...generating angiotatin in vitro comprising contacting plasminogen or plasmin with a plasminogen activator and a **sulfhydryl donor**.

Exemplary Claim:

...generating angiotatin in vitro comprising contacting plasminogen or

plasmin with a plasminogen activator and a **sulfhydryl donor**.

Non-exemplary Claims:

...3. The method of claim 1 wherein the **sulfhydryl donor** is selected from the group consisting of cysteine, N-acetyl cysteine, **captopril**, D-penicillamine, and reduced glutathione...

?

? s captopril

S1 28138 CAPTOPRIL

? s tumor? or cancer? or malignan?

1399882 TUMOR?

1078348 CANCER?

444482 MALIGNAN?

S2 2280773 TUMOR? OR CANCER? OR MALIGNAN?

? s s1 and s2

28138 S1

2280773 S2

S3 711 S1 AND S2

? s s3 and py<1996

Processing

711 S3

27331806 PY<1996

S4 491 S3 AND PY<1996

? s treat? or inhibit?

Processing

3903099 TREAT?

2371705 INHIBIT?

S5 5737036 TREAT? OR INHIBIT?

? s s4 and s5

491 S4

5737036 S5

S6 414 S4 AND S5

? t s6/3,k,ab/1-10

6/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

09490650 95113359 PMID: 7813949

Improvement in scleroderma kidney with **captopril**

Ben David A; Blau A; Rapoport G

Nephrology Dept., Chaim Sheba Medical Center, Tel Hashomer.

Harefuah (ISRAEL) Oct 1994, 127 (7-8) p234-5, 287, ISSN

0017-7768 Journal Code: FZF

Languages: HEBREW

Document type: Journal Article

Record type: Completed

In the past bilateral nephrectomy was often necessary in **treating** hypertensive scleroderma renal crisis. Since the availability of convertin enzyme **inhibitors**, many patients who were dialysis-dependent have recovered sufficiently to discontinue dialysis. We describe a 32-year-old woman with scleroderma who developed **malignant** hypertension and acute renal failure and required dialysis. She was **treated** aggressively with **captopril** and other agents. After 15 months, renal function improved and hemodialysis could be discontinued.

Improvement in scleroderma kidney with **captopril**

Oct 1994,

In the past bilateral nephrectomy was often necessary in **treating** hypertensive scleroderma renal crisis. Since the availability of convertin enzyme **inhibitors**, many patients who were dialysis-dependent have recovered sufficiently to discontinue dialysis. We describe a 32-year-old woman with scleroderma who developed **malignant** hypertension and acute renal failure and required dialysis. She was **treated** aggressively

with **captopril** and other agents. After 15 months, renal function improved and hemodialysis could be discontinued.

Descriptors: **Captopril**--therapeutic use--TU; *Kidney Failure, Acute --drug therapy--DT; *Scleroderma, Systemic--drug therapy--DT; Adult; Hypertension, **Malignant**--complications--CO; Kidney Failure, Acute --complications--CO; Kidney Failure, Acute--therapy--TH; Renal Dialysis; Scleroderma...

Chemical Name: **Captopril**

6/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08907758 96152430 PMID: 8572589

Captopril inhibits glioma cell invasion in vitro: involvement of matrix metalloproteinases.

Nakagawa T; Kubota T; Kabuto M; Koderia T

Department of Neurosurgery, Fukui Medical School, Japan.

Anticancer research (GREECE) Sep-Oct 1995, 15 (5B) p1985-9,

ISSN 0250-7005 Journal Code: 59L

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

We investigated the effects of **captopril** on the activity of matrix metalloproteinases (MMPs) secreted by T98G glioma cells and their invasiveness in vitro. On gelatin zymography, **captopril inhibited** gelatinolytic activities in the culture media of T98G cells. This **inhibitory** effect was reversed by the presence of excess zinc. In an in vitro invasion assay, invasion into the reconstituted basement membrane (Matrigel) by T98G glioma cells was **inhibited** by **captopril** in a dose-dependent manner. This **inhibitory** effect was also reversed by the addition of zinc to the culture media. However, at the effective concentration of **captopril** for the prevention of **tumor** cell invasion it did not **inhibit** the motility, adhesion to Matrigel or proliferation of T98G cells. These findings suggest that **captopril inhibits** the invasiveness of T98G glioma cells due to its MMP **inhibitory** activity, chelating zinc ions at the active center of MMPs.

Captopril inhibits glioma cell invasion in vitro: involvement of matrix metalloproteinases.

Sep-Oct 1995,

We investigated the effects of **captopril** on the activity of matrix metalloproteinases (MMPs) secreted by T98G glioma cells and their invasiveness in vitro. On gelatin zymography, **captopril inhibited** gelatinolytic activities in the culture media of T98G cells. This **inhibitory** effect was reversed by the presence of excess zinc. In an in vitro invasion assay, invasion into the reconstituted basement membrane (Matrigel) by T98G glioma cells was **inhibited** by **captopril** in a dose-dependent manner. This **inhibitory** effect was also reversed by the addition of zinc to the culture media. However, at the effective concentration of **captopril** for the prevention of **tumor** cell invasion it did not **inhibit** the motility, adhesion to Matrigel or proliferation of T98G cells. These findings suggest that **captopril inhibits** the invasiveness of T98G glioma cells due to its MMP **inhibitory** activity, chelating zinc ions at the active center of MMPs.

Descriptors: Angiotensin-Converting Enzyme **Inhibitors**--pharmacology --PD; ***Captopril**--pharmacology--PD; *Gelatinases--antagonists and **inhibitors**--AI; *Glioma--pathology--PA; Dose-Response Relationship, Drug; Gelatinases--physiology--PH; Glioma--drug therapy--DT; Neoplasm Invasiveness; **Tumor** Cells, Cultured; Zinc--pharmacology--PD

Chemical Name: Angiotensin-Converting Enzyme **Inhibitors**; **Captopril**; Zinc; Gelatinases

6/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08860120 94348822 PMID: 8069586

The Caco-2 cell monolayers as an intestinal metabolism model: metabolism of dipeptide Phe-Pro.

Hu M; Chen J; Tran D; Zhu Y; Leonardo G

Department of Pharmaceutical Sciences, College of Pharmacy, Washington State University, Pullman 99164-6510.

Journal of drug targeting (SWITZERLAND) 1994, 2 (1) p79-89,
ISSN 1061-186X Journal Code: B3S

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The metabolism of Phe-Pro was investigated in Caco-2 cell monolayers, a model of small intestinal epithelium. The results indicate that the majority of Phe-Pro was hydrolyzed during passage from the apical (AP) to basolateral (BL) side. The enzyme responsible for the hydrolysis is prolidase, a cytosolic enzyme. Through kinetic studies of a supernatant enzyme preparation, a Km of 30.4 microM and Vmax of 38.9 nmol/min per mg of protein were obtained. The enzyme catalyzed hydrolysis was **inhibited**

by proline (66%), Zn+ (86%), Cu++ (100%), Fe (100%), PCMB (89%), and **captopril** (66%), but not by leucine. We also studied the transcellular transport of Phe-Pro by measuring the amount of Phe in the receiver media. In the presence of a proton gradient (AP pH6, BL pH7.4), the appearance rate of Phe in the BL media after Phe-Pro was loaded apically was at least 100 times faster than that in the AP media after Phe-Pro was loaded basolaterally. The former is also higher than the appearance rate of Phe without a transepithelial proton gradient (pH 6-pH 6) or against a proton gradient (pH7.4-pH6). The rate of appearance of Phe in the BL media (pH7.4) after Phe-Pro was loaded on the AP side (pH 6) was decreased by the presence in the AP media of proline (42%), leucine (40%), and **captopril** (17%), but not by Zn++. In conclusion, the transmembrane uptake of Phe-Pro is dependent on a proton gradient, and the intracellular metabolism of Phe-Pro is complete via hydrolysis by prolidase.

1994,

... 38.9 nmol/min per mg of protein were obtained. The enzyme catalyzed hydrolysis was **inhibited** by proline (66%), Zn+ (86%), Cu++ (100%), Fe (100%), PCMB (89%), and **captopril** (66%), but not by leucine. We also studied the transcellular transport of Phe-Pro by...

... was decreased by the presence in the AP media of proline (42%), leucine (40%), and **captopril** (17%), but not by Zn++. In conclusion, the transmembrane uptake of Phe-Pro is dependent...

; Cell Division--physiology--PH; Chromatography, High Pressure Liquid; Diffusion Chambers, Culture; Dipeptidases--antagonists and **inhibitors** --AI; Dipeptidases--metabolism--ME; Hydrogen-Ion Concentration; Hydrolysis ; Intestines--enzymology--EN; Models, Biological; Subcellular Fractions --enzymology--EN; Temperature; **Tumor** Cells, Cultured

6/3,K,AB/4 (Item 4 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08855749 94189851 PMID: 8141402

Cardiac hypertrophy and brain natriuretic peptide in experimental hypertension.

Kohno M; Fukui T; Horio T; Yokokawa K; Yasunari K; Yoshiyama M; Kurihara N; Takeda T

First Department of Internal Medicine, Osaka City University Medical

School, Japan.

American journal of physiology (UNITED STATES) Feb 1994, 266 (2)
Pt 2) pR451-7, ISSN 0002-9513 Journal Code: 3U8

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The blood pressure was decreased after chronic **treatment** with enalapril, MK-954, and hydralazine in deoxycorticosterone acetate (DOCA)-salt-induced **malignant** hypertension of spontaneously hypertensive rats (SHR); however, ventricular weight and plasma brain natriuretic peptide (BNP) concentration were decreased after enalapril and MK-954 but not after hydralazine. The BNP secretory rates from the ventricle in enalapril- and MK-954-treated DOCA-salt SHR were decreased to approximately 50% of those in untreated DOCA-salt SHR. The BNP secretory rate from the ventricle was positively correlated with ventricular weight in untreated and **treated** DOCA-salt SHR. In contrast, acute administration of **captopril** or MK-954 did not decrease the BNP secretory rate from the heart. Results suggest that the decrease in plasma BNP after enalapril and MK-954 is attributed to a decline in the secretion from the ventricle but not from the atrium. The reduction in ventricular mass appeared to be related to this decline.

Feb 1994,

The blood pressure was decreased after chronic **treatment** with enalapril, MK-954, and hydralazine in deoxycorticosterone acetate (DOCA)-salt-induced **malignant** hypertension of spontaneously hypertensive rats (SHR); however, ventricular weight and plasma brain natriuretic peptide (BNP)...

... not after hydralazine. The BNP secretory rates from the ventricle in enalapril- and MK-954-treated DOCA-salt SHR were decreased to approximately 50% of those in untreated DOCA-salt SHR...

... BNP secretory rate from the ventricle was positively correlated with ventricular weight in untreated and **treated** DOCA-salt SHR. In contrast, acute administration of **captopril** or MK-954 did not decrease the BNP secretory rate from the heart. Results suggest...

...Descriptors: Blood Pressure--drug effects--DE; *Cardiomegaly--physiopathology--PP; *Enalapril--pharmacology--PD; *Hydralazine--pharmacology--PD; *Hypertension, **Malignant**--physiopathology--PP; *Imidazoles--pharmacology--PD; *Nerve Tissue Proteins--blood--BL; *Tetrazoles--pharmacology--PD...; High Pressure Liquid; Creatinine--blood--BL; Desoxycorticosterone; Heart--drug effects--DE; Heart--physiopathology--PP; Hypertension, **Malignant**--blood--BL; Hypertension, **Malignant**--chemically induced--CI; Losartan; Natriuretic Peptide, Brain; Rats; Rats, Inbred SHR; Sodium, Dietary

6/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08779461 97021774 PMID: 8868134

Effects of thiorphan, bestatin and **captopril** on the Lewis lung carcinoma metastases in mice.

Kowalski J; Belowski D; Madej A; Herman ZS

Department of Clinical Pharmacology, Silesian Academy of Medicine, Katowice, Poland.

Polish journal of pharmacology (POLAND) Sep-Oct 1995, 47 (5)

p423-7, ISSN 1230-6002 Journal Code: BT7

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Previously we have found that administration of thiorphan alone or in combination with bestatin exerts antitumor effect in mice, including

reduction of B16 melanoma **tumor** growth and prolongation of survival time. These data prompted us to extend our studies to estimate the effect of **treatment** with thiorphan, **captopril** and bestatin on lung metastases in mice. Administration of thiorphan alone at a dose of 25 micrograms/mouse or in combination with bestatin (50 micrograms) or **captopril** (5 mg/mouse) decreased the number of spontaneous metastases in lungs of Lewis lung carcinoma bearing mice. Neither the injections of bestatin, **captopril** nor bestatin in combination with **captopril** influenced the number of lung **tumor** colonies. **Treatment** with thiorphan at a dose 25 micrograms augmented cytotoxic activity of natural killer (NK) cells and macrophages. These observations explain partly the mechanism of action of thiorphan.

Effects of thiorphan, bestatin and **captopril** on the Lewis lung carcinoma metastases in mice.

Sep-Oct 1995,

... or in combination with bestatin exerts antitumor effect in mice, including reduction of B16 melanoma **tumor** growth and prolongation of survival time. These data prompted us to extend our studies to estimate the effect of **treatment** with thiorphan, **captopril** and bestatin on lung metastases in mice. Administration of thiorphan alone at a dose of 25 micrograms/mouse or in combination with bestatin (50 micrograms) or **captopril** (5 mg/mouse) decreased the number of spontaneous metastases in lungs of Lewis lung carcinoma bearing mice. Neither the injections of bestatin, **captopril** nor bestatin in combination with **captopril** influenced the number of lung **tumor** colonies. **Treatment** with thiorphan at a dose 25 micrograms augmented cytotoxic activity of natural killer (NK) cells...

Descriptors: Angiotensin-Converting Enzyme **Inhibitors**--therapeutic use--TU; ***Captopril**--therapeutic use--TU; *Carcinoma, Lewis Lung --drug therapy--DT; *Leucine--analogs and derivatives--AA; *Neoplasm Metastasis--pathology--PA; *Protease **Inhibitors**--therapeutic use--TU; *Thiorphan--therapeutic use--TU

Chemical Name: Angiotensin-Converting Enzyme **Inhibitors**; Protease **Inhibitors**; bestatin; **Captopril**; Leucine; Thiorphan

6/3,K,AB/6 (Item 6 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08757962 96327975 PMID: 8744684

Effect of **captopril** and thiorphan on the proliferation of human neoplastic cell lines and their influence on cytostatic activity of interferon alpha or cytotoxic activity of doxorubicin.

Kowalski J; Belowski D; Wielgus J; Gabryel B; Klin M; Herman ZS
Department of Clinical Pharmacology, Silesian Medical Academy, Katowice, Poland.

Archivum immunologiae et therapiae experimentalis (POLAND) 1995,
43 (1) p47-50, ISSN 0004-069X Journal Code: 790

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

We have assessed the effect of thiorphan or **captopril** on proliferation of two human **tumor** cell lines, A549 and HL60 including their influence on the cytostatic activity of interferon alpha or doxorubicin. The results showed that **captopril** **inhibits** the proliferation of both A549 and HL60 cells lines but thiorphan has antiproliferative effect only on A549 cells in a dose-dependent manner. However, neither **captopril** nor thiorphan administered in combination with interferon alpha or doxorubicin enhanced cytotoxic potential of doxorubicin and cytostatic activity of interferon alpha.

Effect of **captopril** and thiorphan on the proliferation of human neoplastic cell lines and their influence on cytostatic...

1995,

We have assessed the effect of thiorphan or **captopril** on proliferation of two human **tumor** cell lines, A549 and HL60 including their influence on the cytostatic activity of interferon alpha or doxorubicin. The results showed that **captopril** inhibits the proliferation of both A549 and HL60 cells lines but thiorphan has antiproliferative effect only on A549 cells in a dose-dependent manner. However, neither **captopril** nor thiorphan administered in combination with interferon alpha or doxorubicin enhanced cytotoxic potential of doxorubicin...

Descriptors: Antineoplastic Agents, Combined--pharmacology--PD; ***Captopril**--pharmacology--PD; *Thiorphan--pharmacology--PD; **Captopril**--administration and dosage--AD; Cell Division--drug effects--DE; Doxorubicin--administration and dosage--AD; Drug...

...effects--DE; Interferon Alfa-2b--administration and dosage--AD; Kinetics; Thiorphan--administration and dosage--AD; **Tumor** Cells, Cultured

Chemical Name: Antineoplastic Agents, Combined; Doxorubicin; **Captopril**; Thiorphan; Interferon Alfa-2b

6/3,K,AB/7 (Item 7 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08724985 96188478 PMID: 8608045

An overview cost-utility analysis of prostate **cancer** screening.

Thompson IM; Optenberg SA.

Urology Service Brooke Army Medical Center, Center for Health Care Studies, US Army Medical Department Center and School, San Antonio, Texas, USA.

Oncology (UNITED STATES) Nov 1995, 9 (11 Suppl) p141-5, ISSN 0890-9091 Journal Code: AVP

Languages: ENGLISH

Document type: Journal Article; Review; Review, Tutorial

Record type: Completed

The value of prostate **cancer** screening remains controversial because of the high prevalence of the disease and the fact that many **tumors** detected through screening are not destined to lead to morbidity or mortality, rendering **treatment** unnecessary. An ongoing NCI-sponsored screening trial may eventually put an end to the controversy. However, in the meantime, cost-utility estimates suggest that the cost per crude and quality-adjusted life year gained from prostate **cancer** screening and **treatment** ranges from \$8,400 to \$23,100 (with an estimated 1 to 2.68 QALYs gained from screening and **treatment**), and that these estimates are actually lower than, or well within the range of, the costs of many commonly accepted medical interventions, including screening mammography in women under age 50 (\$232,000) and **treatment** of hypertension with **captopril** (\$82,600) or hydrochlorothiazide (\$23,500). Thus, we conclude that prostate **cancer** screening may indeed be cost effective and should be offered to men in the at-risk age range.

An overview cost-utility analysis of prostate **cancer** screening.

Nov 1995,

The value of prostate **cancer** screening remains controversial because of the high prevalence of the disease and the fact that many **tumors** detected through screening are not destined to lead to morbidity or mortality, rendering **treatment** unnecessary. An ongoing NCI-sponsored screening trial may eventually put an end to the controversy ...

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6/3,K,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08712188 96100018 PMID: 8580368

Angiotensin-converting-enzyme **inhibitors** suppress synthesis of tumour necrosis factor and interleukin 1 by human peripheral blood mononuclear cells.

Schindler R; Dinarello CA; Koch KM

Department of Nephrology, Medical School Hannover, Germany.

Cytokine (UNITED STATES) Aug 1995, 7 (6) p526-33, ISSN 1043-4666 Journal Code: A52

Contract/Grant No.: AI 15614, AI, NIAID

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Administration of angiotensin-converting-enzyme (ACE) **inhibitors** reduce vascular proliferation following endothelial injury as well as progression of renal disease in various animal models. These effects might be due to interference with cytokines such as interleukin 1 (IL-1) or tumour necrosis factor alpha (TNF) since they have been implicated in regulating the effects of vascular cell growth factors such as fibroblast- and platelet-derived growth factors. We investigated the in vitro synthesis of IL-1 and TNF from human peripheral blood mononuclear cells (PBMC) in the presence of various ACE-**inhibitors**. **Captopril** dose-dependently suppressed the IL-1 beta-induced synthesis of TNF by 74% ($P < 0.01$) and the IL-1 beta-induced synthesis of IL-1 alpha by 60% ($P < 0.01$). Cytokine synthesis induced by lipopolysaccharide was less affected. At concentrations suppressing TNF and IL-1, **captopril** did not reduce the synthesis of complement C3 in the same cells. Enalapril and cilazapril also suppressed cytokine-induced cytokine synthesis. Ramipril, lisinopril, perindopril and spirapril had no significant effect on TNF synthesis suggesting that the effect was not related specifically to the **inhibition** of ACE. Accumulation of mRNA for IL-1 and TNF were not affected by **captopril**, suggesting a posttranscriptional effect. We conclude that certain ACE-**inhibitors** suppress IL-1 and TNF synthesis at a posttranscriptional level and might therefore influence cytokine-mediated cell growth.

Angiotensin-converting-enzyme **inhibitors** suppress synthesis of tumour necrosis factor and interleukin 1 by human peripheral blood mononuclear cells.

Aug 1995,

Administration of angiotensin-converting-enzyme (ACE) **inhibitors** reduce vascular proliferation following endothelial injury as well as progression of renal disease in various...

... and TNF from human peripheral blood mononuclear cells (PBMC) in the presence of various ACE-**inhibitors**. **Captopril** dose-dependently suppressed the IL-1 beta-induced synthesis of TNF by 74% ($P < 0.01$).

... Cytokine synthesis induced by lipopolysaccharide was less affected. At concentrations suppressing TNF and IL-1, **captopril** did not reduce the synthesis of complement C3 in the same cells. Enalapril and cilazapril...

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posttranscriptional effect. We conclude that certain ACE-inhibitors suppress IL-1 and TNF synthesis at a posttranscriptional level and might therefore influence cytokine...

Descriptors: Angiotensin-Converting Enzyme **Inhibitors**--pharmacology
--PD; *Interleukin-1--physiology--PH; *Leukocytes, Mononuclear --drug effects--DE; ***Tumor** Necrosis Factor--physiology--PH; **Captopril**
--pharmacology--PD; Depression, Chemical; Gene Expression; Interleukin-1
--genetics--GE; Interleukin-1--metabolism--ME; Leukocytes, Mononuclear
--metabolism--ME; Transcription, Genetic; **Tumor** Necrosis Factor
--genetics--GE; **Tumor** Necrosis Factor--metabolism--ME
Chemical Name: Angiotensin-Converting Enzyme **Inhibitors**;
Interleukin-1; **Tumor** Necrosis Factor; **Captopril**

6/3,K,AB/9 (Item 9 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

1122

08688002 96128033 PMID: 8539259

Inhibitors of angiotensin-converting enzyme modulate mitosis and gene expression in pancreatic **cancer** cells.

Reddy MK; Baskaran K; Molteni A

Department of Pathology, Northwestern University Medical School, Chicago, Illinois 60611-3008, USA.

Proceedings of the Society for Experimental Biology and Medicine (UNITED STATES) Dec 1995, 210 (3) p221-6, ISSN 0037-9727

Journal Code: PXZ

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The angiotensin-converting enzyme (ACE) **inhibitor captopril** **inhibits** mitosis in several cell types that contain ACE and renin activity. In the present study, we evaluated the effect of the ACE **inhibitors captopril** and CGS 13945 (10⁻⁸ to 10⁻² M) on proliferation and gene expression in hamster pancreatic duct carcinoma cells in culture. These cells lack renin and ACE activity. Both ACE **inhibitors** produced a dose-dependent reduction in **tumor** cell proliferation within 24 hr. **Captopril** at a concentration of 0.36 mM and CGS 13945 at 150 microM decreased cellular growth rate to approximately half that of the control. Neither drug influenced the viability or the cell cycle distribution of the **tumor** cells. Slot blot analysis of mRNA for four genes, proliferation associated cell nuclear antigen (PCNA), K-ras, protein kinase C-beta (PKC-beta) and carbonic anhydrase II (CA II) was performed. Both ACE **inhibitors** increased K-ras expression by a factor of 2, and had no effect on CA II mRNA levels. **Captopril** also lowered PCNA by 40% and CGS 13945 lowered PKC-beta gene expression to 30% of the control level. The data demonstrate that ACE **inhibitors** exhibit antimitotic activity and differential gene modulation in hamster pancreatic duct carcinoma cells. The absence of renin and ACE activity in these cells suggests that the antimitotic action of **captopril** and CGS 13945 is independent of renin-angiotensin regulation. The growth **inhibition** may occur through downregulation of growth-related gene expression.

Inhibitors of angiotensin-converting enzyme modulate mitosis and gene expression in pancreatic **cancer** cells.

Dec 1995,

The angiotensin-converting enzyme (ACE) **inhibitor captopril** **inhibits** mitosis in several cell types that contain ACE and renin activity. In the present study, we evaluated the effect of the ACE **inhibitors captopril** and CGS 13945 (10⁻⁸ to 10⁻² M) on proliferation and gene expression in...
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Descriptors: Adenocarcinoma--pathology--PA; *Angiotensin-Converting Enzyme **Inhibitors**--pharmacology--PD; ***Captopril**--pharmacology--PD; *Indoles--pharmacology--PD; *Pancreatic Neoplasms--pathology--PA...; DE; Hamsters; Mesocricetus; Mitosis--drug effects--DE; RNA, Messenger--analysis--AN; RNA, Neoplasm--analysis--AN; **Tumor** Cells, Cultured
Chemical Name: Angiotensin-Converting Enzyme **Inhibitors**; Indoles; RNA, Messenger; RNA, Neoplasm; **Captopril**; CGS 13945

6/3,K,AB/10 (Item 10 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08552508 95329096 PMID: 7605341

The prooxidant properties of **captopril**.

Lapenna D; De Gioia S; Mezzetti A; Ciofani G; Di Ilio C; Cuccurullo F
Istituto di Fisiopatologia Medica, Universita degli Studi "G. D'Annunzio", Facolta' di Medicina e Chirurgia, Chieti, Italy.

Biochemical pharmacology (ENGLAND) Jun 29 1995, 50 (1) p27-32,
ISSN 0006-2952 Journal Code: 924

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The thiol drug **captopril** has been reported to possess reducing and transition metal-binding properties, which could result in specific changes in iron and copper prooxidant capacity. Thus, the effects of **captopril** on iron- and copper-induced oxidative injury were evaluated using deoxyribose as the oxidizable substrate in the presence of physiological phosphate concentrations but in the absence of the non-physiological chelator EDTA. In an iron(III)/H₂O₂/ascorbate oxidant system, **captopril** enhanced deoxyribose oxidation only when it was pre-mixed with iron, whereas it did not influence sugar degradation when not pre-mixed with the metal or when ascorbate was omitted. The physiological thiol GSH acted in a similar manner, whereas the SH-lacking angiotensin-converting enzyme **inhibitor** ramiprilat did not influence iron-induced deoxyribose oxidation, indicating that the thiol group is crucial in favouring enhanced iron reactivity due to 'malignant' chelation. Further specific experiments designed to evaluate possible thiol-dependent iron(III) reduction failed to demonstrate ferric to ferrous reduction by either **captopril** or reduced glutathione (GSH). When iron(III) was replaced by copper(II) to induce deoxyribose oxidation, **captopril** was prooxidant both in the presence and absence of ascorbate, and when pre-mixed or not with copper. On the other hand, GSH was prooxidant up to 2:1 molar ratio with respect to copper but markedly **inhibited** copper-dependent sugar oxidation beginning at molar ratio of 4:1. Ramiprilat did not significantly influence copper-induced deoxyribose oxidation. Moreover, unlike the experiments performed with iron, **captopril**, as well as GSH, readily reduced copper(II) to copper(I). Hence, **captopril** can act as prooxidant in the presence of iron or copper. In the former case, only 'malignant' iron chelation

by the drug is involved in oxidant injury, whereas in the latter both copper chelation and reduction are operative, although specific chelating mechanisms are crucial in enhancing copper-induced oxidant injury. **Captopril**, therefore, cannot be considered simply as an 'antioxidant drug', and its catalytic transition metal-related prooxidant capacity should be taken into account in experimental and clinical investigations.

The prooxidant properties of **captopril**.

Jun 29 1995,

The thiol drug **captopril** has been reported to possess reducing and transition metal-binding properties, which could result in specific changes in iron and copper prooxidant capacity. Thus, the effects of **captopril** on iron- and copper-induced oxidative injury were evaluated using deoxyribose as the oxidizable substrate...

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... physiological thiol GSH acted in a similar manner, whereas the SH-lacking angiotensin-converting enzyme **inhibitor** ramiprilat did not influence iron-induced deoxyribose oxidation, indicating that the thiol group is crucial in favouring enhanced iron reactivity due to 'malignant' chelation. Further specific experiments designed to evaluate possible thiol-dependent iron(III) reduction failed to demonstrate ferric to ferrous reduction by either **captopril** or reduced glutathione (GSH). When iron(III) was replaced by copper(II) to induce deoxyribose oxidation, **captopril** was prooxidant both in the presence and absence of ascorbate, and when pre-mixed or...

... GSH was prooxidant up to 2:1 molar ratio with respect to copper but markedly **inhibited** copper-dependent sugar oxidation beginning at molar ratio of 4:1. Ramiprilat did not significantly influence copper-induced deoxyribose oxidation. Moreover, unlike the experiments performed with iron, **captopril**, as well as GSH, readily reduced copper(II) to copper(I). Hence, **captopril** can act as prooxidant in the presence of iron or copper. In the former case, only 'malignant' iron chelation by the drug is involved in oxidant injury, whereas in the latter both...

... reduction are operative, although specific chelating mechanisms are crucial in enhancing copper-induced oxidant injury. **Captopril**, therefore, cannot be considered simply as an 'antioxidant drug', and its catalytic transition metal-related...

Descriptors: **Captopril**--pharmacology--PD; *Reactive Oxygen Species --pharmacology--PD; **Captopril**--chemistry--CH; Copper--chemistry--CH; Deoxyribose--chemistry--CH; Iron--chemistry--CH; Oxidation-Reduction; Reactive Oxygen...

Chemical Name: Reactive Oxygen Species; Deoxyribose; **Captopril**; Iron; Copper

?

alog Acc No: 2016646 IFI Acc No: 9002471

Document Type: C

INHIBITING OF **TUMOR** GROWTH WITH AN ANTAGONIST OF THE
RENIN-ANGIOTEN-SIN SYSTEM

Inventors: Fernandez Leonardo A (US)

Assignee: Clinipad Corp The Assignee Code: 22507 Document Type:
REASSIGNED

Publication (No,Date), Applic (No,Date)

US 4898732 19900206 US 88190158 19880504

Publication Kind: A

Calculated Expiration: 20080504

(Cited in 007 later patents) Document Type: EXPIRED

Priority Applic(No,Date): US 88190158 19880504

Abstract:

A method of inhibiting **tumor** growth in a patient which comprises
administering to the patient an effective dose of a pharmaceutical
antagonist of the renin-angiotensin system of the patient.

INHIBITING OF **TUMOR** GROWTH WITH AN ANTAGONIST OF THE
RENIN-ANGIOTEN-SIN SYSTEM

Abstract:

A method of inhibiting **tumor** growth in a patient which comprises
administering to the patient an effective dose of a...

Non-exemplary Claims:

...The method of claim 1, in which said controlled-release member is
implanted at a **tumor** site...

...7. The method of claim 2 in which said pharmaceutical antagonist is
captopril.

? ds

Set	Items	Description
S1	28138	CAPTOPRIL
S2	2280773	TUMOR? OR CANCER? OR MALIGNAN?
S3	711	S1 AND S2
S4	491	S3 AND PY<1996
S5	5737036	TREAT? OR INHIBIT?
S6	414	S4 AND S5

? s plasminogen

S7 80704 PLASMINOGEN
? s s1 and s7

28138 S1
80704 S7
S8 246 S1 AND S7
? s s8 and py<=1996

Processing

246 S8
29341310 PY<=1996
S9 182 S8 AND PY<=1996
? s s9 and s2

182 S9
2280773 S2
S10 12 S9 AND S2
? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
S11 12 RD (unique items)

? s captopril

S1 28138 CAPTOPRIL
? s metastas?

S2 256835 METASTAS?
? s s1 and s2

28138 S1
256835 S2
S3 23 S1 AND S2
? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
S4 15 RD (unique items)
? s s4 and py<=1996

Processing

15 S4
29341310 PY<=1996
S5 8 S4 AND PY<=1996
? t s5/3,k,ab/1-5

5/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

08779461 97021774 PMID: 8868134

Effects of thiorphan, bestatin and **captopril** on the Lewis lung carcinoma **metastases** in mice.

Kowalski J; Belowski D; Madej A; Herman ZS
Department of Clinical Pharmacology, Silesian Academy of Medicine,
Katowice, Poland.

Polish journal of pharmacology (POLAND) Sep-Oct 1995, 47 (5)
p423-7, ISSN 1230-6002 Journal Code: BT7

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Previously we have found that administration of thiorphan alone or in combination with bestatin exerts antitumor effect in mice, including reduction of B16 melanoma tumor growth and prolongation of survival time. These data prompted us to extend our studies to estimate the effect of treatment with thiorphan, **captopril** and bestatin on lung **metastases** in mice. Administration of thiorphan alone at a dose of 25 micrograms/mouse or in combination with bestatin (50 micrograms) or **captopril** (5 mg/mouse) decreased the number of spontaneous **metastases** in lungs of Lewis lung carcinoma bearing mice. Neither the injections of bestatin, **captopril** nor bestatin in combination with **captopril** influenced the number of lung tumor colonies. Treatment with thiorphan at a dose 25 micrograms augmented cytotoxic activity of natural killer (NK) cells and macrophages. These observations explain partly the mechanism of action of thiorphan.

Effects of thiorphan, bestatin and **captopril** on the Lewis lung carcinoma **metastases** in mice.

Sep-Oct 1995,

... data prompted us to extend our studies to estimate the effect of treatment with thiorphan, **captopril** and bestatin on lung **metastases** in mice. Administration of thiorphan alone at a dose of 25 micrograms/mouse or in combination with bestatin (50 micrograms) or

captopril (5 mg/mouse) decreased the number of spontaneous **metastases** in lungs of Lewis lung carcinoma bearing mice. Neither the injections of bestatin, **captopril** nor bestatin in combination with **captopril** influenced the number of lung tumor colonies. Treatment with thiorphan at a dose 25 micrograms...

Descriptors: Angiotensin-Converting Enzyme Inhibitors--therapeutic use --TU; ***Captopril**--therapeutic use--TU; *Carcinoma, Lewis Lung--drug therapy--DT; *Leucine--analogs and derivatives--AA; *Neoplasm **Metastasis**--pathology--PA; *Protease Inhibitors--therapeutic use--TU; *Thiorphan--therapeutic use--TU

Chemical Name: Angiotensin-Converting Enzyme Inhibitors; Protease Inhibitors; bestatin; **Captopril**; Leucine; Thiorphan

5/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

04926417 85048631 PMID: 6437662

Recovery from mitomycin C-induced hemolytic uremic syndrome. A case report.

Verwey J; Boven E; van der Meulen J; Pinedo HM
Cancer (UNITED STATES) Dec 15 1984, 54 (12) p2878-81, ISSN
0008-543X Journal Code: CLZ
Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Mitomycin C (MMC) is a cytotoxic agent that may induce a hemolytic uremic syndrome (HUS) with severe renal insufficiency. Of all reported patients with terminal renal failure only two survived with chronic hemodialysis. A patient with advanced gastric cancer in complete remission, who developed MMC-induced HUS, is reported; hemodialysis was necessary because of oliguria. Hemolysis subsided, and after addition of **captopril** renal function recovered partially. The patient is alive 6 months after discontinuation of hemodialysis. Recently she developed brain **metastases**. Symptoms of hemolysis did not recur. The pathogenesis and treatment of HUS are discussed.

Dec 15 1984,

... HUS, is reported; hemodialysis was necessary because of oliguria. Hemolysis subsided, and after addition of **captopril** renal function recovered partially. The patient is alive 6 months after discontinuation of hemodialysis. Recently she developed brain **metastases**. Symptoms of hemolysis did not recur. The pathogenesis and treatment of HUS are discussed.

5/3,K,AB/3 (Item 1 from file: 55)
DIALOG(R) File 55:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

09246728 BIOSIS NO.: 199497255098

Captopril reduces the incidence, growth and mitotic activity of radiation-induced fibrosarcomas in rats.

AUTHOR: Ward W F; Molteni A; Ts'ao C; Taylor J M

AUTHOR ADDRESS: Dep. Radiol., Northwestern Univ. Med. Sch., Chicago, IL 60611**USA

JOURNAL: FASEB Journal 8 (4-5):pA672 1994

CONFERENCE/MEETING: Experimental Biology 94, Parts I and II Anaheim, California, USA April 24-28, 1994

ISSN: 0892-6638

RECORD TYPE: Citation

LANGUAGE: English

1994

Captopril reduces the incidence, growth and mitotic activity of radiation-induced fibrosarcomas in rats.

1994

...REGISTRY NUMBERS: **CAPTOPRIL**

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: **CAPTOPRIL**

MISCELLANEOUS TERMS: ...**CAPTOPRIL**; ...

...**METASTASIS**;

5/3,K,AB/4 (Item 2 from file: 55)

DIALOG(R)File 55:Biosis Previews(R)

(c) 2002 BIOSIS. All rts. reserv.

09246717 BIOSIS NO.: 199497255087

Captopril modulates hormone receptor concentration and inhibits proliferation of human mammary ductal carcinoma cells in culture.

AUTHOR: Small W Jr; Ward W F; Molteni A; Kim Y T; Goolsby C L; Taylor J M; Speck G

AUTHOR ADDRESS: Northwestern Univ. Med. Sch., Chicago, IL 60611**USA

JOURNAL: FASEB Journal 8 (4-5):pA670 1994

CONFERENCE/MEETING: Experimental Biology 94, Parts I and II Anaheim, California, USA April 24-28, 1994

ISSN: 0892-6638

RECORD TYPE: Citation

LANGUAGE: English

1994

Captopril modulates hormone receptor concentration and inhibits proliferation of human mammary ductal carcinoma cells in culture.

1994

...REGISTRY NUMBERS: **CAPTOPRIL**

DESCRIPTORS:

CHEMICALS & BIOCHEMICALS: **CAPTOPRIL**

MISCELLANEOUS TERMS: ...**CAPTOPRIL**; ...

...**METASTASIS**;

5/3,K,AB/5 (Item 1 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

(c) 2002 Inst for Sci Info. All rts. reserv.

05234444 Genuine Article#: VK243 Number of References: 28

Title: ENZYMATIC DIGESTION OF BRADYKININ BY RAT SERTOLI-CELL CULTURES (Abstract Available)

Author(s): MONSEES TK; MISKA W; SCHILL WB

Corporate Source: UNIV GIESSEN,DEPT DERMATOL & ANDROL,GAFFKYSTR 14/D-35385 GIESSEN//GERMANY/

Journal: JOURNAL OF ANDROLOGY, 1996, V17, N4 (JUL-AUG), P375-381

ISSN: 0196-3635

Language: ENGLISH Document Type: ARTICLE

Abstract: Sertoli cells play a key role in spermatogenesis. To study the involvement of the kallikrein-kinin system in the testis, the pattern of bradykinin-inactivating kininases in rat Sertoli cells was investigated. Exogenous bradykinin (Arg(1)-Pro(2)-Pro(3)-Gly(4)-Phe(5)-Ser(6)-Pro(7)-Phe(8)-Arg(9)) is cleaved at Pro(7)-Phe(8), Phe(5)-Ser(6), and Gly(4)-Phe(5), as demonstrated by high performance liquid chromatography analysis. Degradation of bradykinin was strongly inhibited by phosphoramidon and thiorphan, which are specific inhibitors of neutral metalloendopeptidase-24.11. The kininase type II-specific inhibitors, **captopril** and enalapril, were only partially effective in preventing peptidolysis. This indicates that the main kininases responsible for rapid bradykinin inactivation are neutral

metalloendopeptidase and, to a lesser extent, kininase type II. Neutral metalloendopeptidase and kininase type II were shown to be located on Sertoli cell membranes. A low degree of bradykinin degradation was detected by simultaneous inhibition of neutral metalloendopeptidase-24.11 and kininase II, pointing out the involvement of further peptidases with minor activities. This remaining activity is probably not due to the action of kininase type I or cysteine proteases, as shown by specific inhibitors. The data presented indicate the occurrence of membrane-bound kininases, which are an important part of the kallikrein-kinin system, in rat Sertoli cell cultures.

, 1996

...Abstract: which are specific inhibitors of neutral metalloendopeptidase-24.11. The kininase type II-specific inhibitors, **captopril** and enalapril, were only partially effective in preventing peptidolysis. This indicates that the main kininases...
...Research Fronts: RESPONSES; FUNCTIONAL EXPRESSION)
94-0512 001 (SERTOLI CELLS; BASEMENT-MEMBRANE REGULATION; HORMONE-DEPENDENT BREAST-CANCER; **METASTASIS** OF LEWIS LUNG-CARCINOMA; ENDOMETRIAL TISSUE; MALIGNANT PHENOTYPE)

?

ialog Acc No: 2092816 IFI Acc No: 9024465

Document Type: C

METHODS AND COMPOSITIONS FOR THROMBOLYTIC THERAPY; FACTOR VIIIA INHIBITOR

Inventors: Claremon David A (US); Friedman Paul A (US); Remy David C (US);

Stern Andrew M (US)

Assignee: Merck & Co Inc Assignee Code: 54136

Publication (No,Date), Applic (No,Date)

US 4968494 19901106 US 90507013 19900410

Publication Kind: A

Calculated Expiration: 20071106

(Cited in 009 later patents) Document Type: EXPIRED

Continuation Pub(No), Applic(No,Date): ABANDONED

US 8732123

19870327

Priority Applic(No,Date): US 90507013 19900410; US 8732123 19870327

Abstract:

Certain Factor XIIIa inhibitor compounds have been discovered which have been found to be useful in the lysis of blood clots and thus adaptable for administration in thrombolytic therapy either alone or together with **plasminogen activator**.

Abstract:

...blood clots and thus adaptable for administration in thrombolytic therapy either alone or together with **plasminogen activator**.

Non-exemplary Claims:

...3. A composition according to claim 1 which also contains a **plasminogen activator**.

...

...5. A method according to claim 4 wherein a **plasminogen activator** is also administered...

...6. A method according to claim 5 wherein the **plasminogen activator** is **tissue plasminogen activator**.

...

...7. A method according to claim 5 wherein the **plasminogen activator** is selected from the group consisting of **tissue**

7/3,K,AB/34 (Item 6 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent
(c) 2002 IFI/CLAIMS(R). All rts. reserv.

Dialog Acc No: 3214993 IFI Acc No: 9933315

Document Type: C

HYBRID MATRIX IMPLANTS AND EXPLANTS; IMPLANTABLE DEVICE HAVING A BODY OF
MATRIX MATERIAL MADE OF INSOLUBLE COLLAGEN FIBRILS, WITH CULTURED
VERTEBRATE CELLS GENETICALLY ENGINEERED TO EXPRESS A MEDICALLY USEFUL
PEPTIDE AND ALSO MICROSPHERES EMBEDDED WITHIN THE MATRIX

Inventors: Mineau-Hanschke Rochelle (US)

Assignee: Transkaryotic Therapies Inc Assignee Code: 40420

Publication (No,Date), Applic (No,Date)

US 5965125 19991012 US 95548002 19951025

Publication Kind: A

Calculated Expiration: 20151025

Priority Applic(No,Date): US 95548002 19951025

Abstract:

An implantable device having a body of matrix material made up of insoluble collagen fibrils, and disposed therewithin (a) a plurality of vertebrate cells; and (b) a plurality of microspheres each of which consists primarily of one or more of the following materials: collagen, polystyrene, dextran, polyacrylamide, cellulose, calcium alginate, latex, polysulfone, or glass.

Publication (No,Date), Applic (No,Date)

... 19991012

Non-exemplary Claims:

...7. The composition of claim 4, wherein the polypeptide is an
angiogenesis factor...

...endothelial cell growth factor, platelet derived growth factor (PDGF),
transforming growth factors, endothelial cell stimulating
angiogenesis factor (ESAF), **angiogenin**, tissue
plasminogen activator (t-PA), granulocyte colony stimulating
factor (G-CSF), and granulocyte-macrophage colony stimulating factor (GM

ialog Acc No: 3434052 IFI Acc No: 0042828
Document Type: C
METHOD FOR TRANSFERRING GENES TO THE HEART USING AAV VECTORS; DNA AND ADEO
VIRUSES WITH VECTORS
Inventors: Diethrich Edward B (US); Kaplitt Martin J (US); Kaplitt Michael
G (US)
Assignee: Rockefeller University Assignee Code: 03137
Publication (No,Date), Applic (No,Date)
US 6162796 20001219 US 95534351 19950927
Publication Kind: A
Calculated Expiration: 20150927
Priority Applic(No,Date): US 95534351 19950927

Abstract:

The invention relates to the use of adeno-associated virus vectors for the transfer of genes to the heart and vasculature. The vector preferably contains a gene encoding a protein which improves heart and vascular function during heart failure. In a specific embodiment, the vector is introduced into the heart and vasculature via a catheter, with the aid of fluoroscopy. The method and vectors for use therein provide for safe and stable gene expression of the transferred genes.

Publication (No,Date), Applic (No,Date)

... 20001219

Non-exemplary Claims:

...5. The method of claim 4, wherein the protein is **streptokinase**, **urokinase** or tissue **plasminogen activator**.

...

...method of claim 1, wherein the expressible gene encodes a protein which is involved in **angiogenesis**.

...

...of delivering an adeno-associated virus vector to a cell of a mammalian heart, comprising **administering** said vector via a catheter inserted into a peripheral artery and delivering said vector to

7/3,K,AB/32 (Item 4 from file: 340)
DIALOG(R) File 340:CLAIMS(R)/US Patent
(c) 2002 IFI/CLAIMS(R). All rts. reserv.

Dialog Acc No: 3357797 IFI Acc No: 0023154

Document Type: C

BENZOTHIOPHENE DERIVATIVES, THEIR PREPARATION AND USE AS **UROKINASE** INHIBITORS; AN ENZYME INHIBITOR TREATING **ANGIOGENESIS**, ARTHRITIS, INFLAMMATION, METASTASIS, OSTEOPOROSIS, TUMORSANGIOGENESIS-DEPENDENT RETINOPATHIES, CONTRACEPTIVE

Inventors: Mizuno Hiroaki (JP); Sakurai Minoru (JP); Tanaka Akito (JP)

Assignee: Fujisawa Pharmaceutical Co Ltd JP Assignee Code: 32600

Publication (No,Date), Applic (No,Date)

US 6093710 20000725 US 99147812 19990312

Publication Kind: A

PCT Pub(No,Date),Applic(No,Date): WO 9811089 19980319 WO
97JP3215 19970912

Section 371: 19990312

Section 102(e):19990312

Priority Applic(No,Date): AU 962278 19960913

Abstract:

A compound of the formula

FIG-01

in which R1 is hydrogen, lower alkyl, optionally substituted ar(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, protected carboxy(lower)alkyl, carboxy(lower)alkyl, hydroxy(lower)alkyl, optionally substituted lower alkylcarbamoyl(lower)alkyl, lower alkylthio(lower)alkyl, carboxy(lower)alkanoyl, protected carboxy(lower)alkanoyl, aroyl, lower alkanoyl, or optionally substituted arylcarbamoyl(lower)alkyl, R2 is hydrogen, carboxy, protected carboxy, formyl or N-(lower)alkyl-N-(lower)alkoxycarbamoyl, R3 is hydrogen or amidino-protective group, A is lower alkylene or carbonyl, X is .

FIG-02

Y is --S-- or --SO2 --, Z is --S-- or --O--, or pharmaceutically acceptable salts thereof which is useful as a medicament.

BENZOTHIOPHENE DERIVATIVES, THEIR PREPARATION AND USE AS **UROKINASE** INHIBITORS...

...AN ENZYME INHIBITOR TREATING **ANGIOGENESIS**, ARTHRITIS, INFLAMMATION, METASTASIS, OSTEOPOROSIS, TUMORSANGIOGENESIS-DEPENDENT RETINOPATHIES, CONTRACEPTIVE

7/3,K,AB/22 (Item 13 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2002 Inst for Sci Info. All rts. reserv.

05356880 Genuine Article#: VT378 Number of References: 34
Title: RETINAL CONTROL ON THE AXIAL LENGTH MEDIATED BY TRANSFORMING
GROWTH-FACTOR-BETA IN CHICK EYE (Abstract Available)
Author(s): HONDA S; FUJII S; SEKIYA Y; YAMAMOTO M
Corporate Source: KOBE UNIV,SCH MED,DEPT OPHTHALMOL,CHUO KU,KUSUNOKI CHO
7-5-2/KOBE/HYOGO 650/JAPAN/
Journal: INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, 1996, V37, N12
(NOV), P2519-2526
ISSN: 0146-0404

Language: ENGLISH Document Type: ARTICLE

Abstract: Purpose. To clarify retinal control on scleral growth in
form-deprivation myopia (FDM) in the chick, the authors studied change
in transforming growth factor-beta (TGF-beta) in the form-deprived eye
and the effect of this growth factor on scleral cell proliferation and
axial length.

Methods. Change in TGF-beta in FDM in the chick was measured by
reverse transcriptase polymerase chain reaction (RT-PCR), immunoblot,
and immunohistochemistry. The effect of TGF-beta on [H-3] thymidine
uptake of scleral chondrocytes was determined by organ culture.

Urokinase plasminogen activator (uPA) and
plasminogen activator inhibitor-1 (PAI-1) were
administered to determine the effect of TGF-beta activation on
the axial length in normal and FDM eyes.

Results. The content of TGF-beta messenger RNA (mRNA) and the
active form of TGF-beta protein were reduced in FDM eyes compared with
the control specimen. Reduced immunoreactivity of TGF

? s (administer? or inject?) (5n) (plasminogene(w) activator)

454918 ADMINISTER?
885066 INJECT?
79 PLASMINOGENE
152339 ACTIVATOR

S1 0 (ADMINISTER? OR INJECT?) (5N) (PLASMINOGENE(W) ACTIVATOR)

? s (administer? or inject?) (5n) (plasminogen(w) activator)

454918 ADMINISTER?
885066 INJECT?
80657 PLASMINOGEN
152339 ACTIVATOR

S2 703 (ADMINISTER? OR INJECT?) (5N) (PLASMINOGEN(W) ACTIVATOR)

? s cancer

S3 1035736 CANCER

? s s2 and s3

703 S2
1035736 S3

S4 11 S2 AND S3

? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.

...completed examining records

S5 9 RD (unique items)

? t s5/3,k,ab/1-9

5/3,K,AB/1 (Item 1 from file: 155)

DIALOG(R) File 155:MEDLINE(R)

08432482 94226369 PMID: 8172379

A case of acute myocardial infarction. Intracoronary thrombosis in two major coronary arteries due to hormone therapy.

Nakagawa T; Yasuno M; Tanahashi H; Ohnishi S; Nishino M; Yamada Y; Abe H
Division of Cardiology, Osaka Rosai Hospital, Japan.

Angiology (UNITED STATES) May 1994, 45 (5) p333-8, ISSN 0003-3197
Journal Code: 4UA

Languages: ENGLISH

Document type: Journal Article; Review; Review of Reported Cases

Record type: Completed

A fifty-four-year-old woman was admitted to the hospital for a sensation of tightness in the chest of one hour's duration. She had undergone surgery for breast **cancer** two years previously and had been taking 30 mg of tamoxifen and 1200 mg of medroxyprogesterone daily after surgery. Emergency coronary angiography on admission revealed thrombi in both the right coronary artery and the left anterior descending coronary artery. Tissue-type **plasminogen activator** was injected into both coronary arteries, resulting in diminution of thrombus size. Repeat coronary angiography on the next day disclosed no thrombus in either artery and no significant stenosis. Electrocardiographic and laboratory data indicated myocardial infarction. These findings strongly suggest that the combination hormone therapy altered the patient's blood coagulability and played an important role in the formation of the intracoronary thrombi and subsequent acute myocardial infarction.

... tightness in the chest of one hour's duration. She had undergone surgery for breast **cancer** two years previously and had been taking 30 mg of tamoxifen and 1200 mg of ...

... in both the right coronary artery and the left anterior descending coronary artery. Tissue-type **plasminogen activator** was **injected** into both coronary arteries, resulting in diminution of thrombus size. Repeat coronary angiography on the...

5/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03518179 77125030 PMID: 1071174

Experiences in treatment of locally advanced breast **cancer** with various combined treatment. A trial to improve the effectiveness of arterial infusion **cancer** chemotherapy.

Ogawa S; Okawa T; Kaneta K; Tsuya A; Utsunomiya J
Nippon Igaku Hoshasen Gakkai zasshi (JAPAN) Dec 25 1976, 36 (12)
p1069-81, ISSN 0048-0428 Journal Code: O3G
Languages: JAPANESE
Document type: Journal Article
Record type: Completed

Experiences in treatment of locally advanced breast **cancer** with various combined treatment. A trial to improve the effectiveness of arterial infusion **cancer** chemotherapy.

...; drug therapy--DT; Breast Neoplasms--radiotherapy--RT; Drug Therapy, Combination; Fluorouracil--administration and dosage--AD; **Injections**, Intra-Arterial; Middle Age; Urinary **Plasminogen Activator** --administration and dosage--AD

5/3,K,AB/3 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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08480774 Genuine Article#: 290JW Number of References: 27

Title: Generation of high-affinity rabbit polyclonal antibodies to the murine urokinase receptor using DNA immunization (ABSTRACT AVAILABLE)

Author(s): Gardsvoll H; Solberg H; Dano K; HoyerHansen G (REPRINT)

Corporate Source: RIGSHOSP, FINSEN LAB, STRANDBLVD 49/DK-2100 COPENHAGEN

O//DENMARK/ (REPRINT); RIGSHOSP, FINSEN LAB/DK-2100 COPENHAGEN

O//DENMARK/

Journal: JOURNAL OF IMMUNOLOGICAL METHODS, 2000, V234, N1-2 (FEB 3), P 107-116

ISSN: 0022-1759 Publication date: 20000203

Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS

Language: English Document Type: ARTICLE

Abstract: The urokinase receptor (uPAR) is a glycolipid anchored cell surface glycoprotein that plays a central role in extracellular proteolysis during tissue remodeling processes and **cancer** invasion. By intramuscular (i.m.) injection of rabbits with plasmid DNA coding for a carboxy-terminally truncated secreted form of the murine uPAR (muPAR), specific anti-sera with a titer of 64,000, as measured by ELISA, have been obtained. Rabbits received a total of 10 monthly injections of 1 mg DNA in phosphate-buffered saline. The antibody titer peaked between the 5th and 7th injection and slowly declined after the 8th injection. After the final immunization the immune response persisted for at least 6 months without further injections. The antibodies generated by DNA immunization were useful for immunohistochemistry and immunoblotting, recognizing the antigen both in its native and in its reduced and alkylated form. Using the antibodies in immunoblotting muPAR was identified in lysates of peritoneal macrophages, spleen and lung tissue. Both the intact and cleaved form of muPAR were identified in lysates of a murine monocyte cell line P388D.1. No cross-reaction with human uPAR was observed. In

immunohistochemical analysis of normal mouse lung tissue uPAR immunoreactivity was located in the alveoli and pulmonary vessels, whereas the bronchial epithelium was negative. These results demonstrate that DNA immunization of rabbits using i.m. injection is a very effective and easy method to raise polyclonal antibodies which can be used for characterization and localization of muPAR in mouse tissue.
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...Abstract: surface glycoprotein that plays a central role in extracellular proteolysis during tissue remodeling processes and cancer invasion. By intramuscular (i.m.) injection of rabbits with plasmid DNA coding for a carboxy...
...Identifiers--LINKED-IMMUNOSORBENT-ASSAY; CELL-SURFACE RECEPTOR; PLASMINOGEN-ACTIVATOR; EXPRESSION; MOUSE; RESPONSES; INJECTION; SEQUENCES

5/3,K,AB/4 (Item 2 from file: 34)
DIALOG(R) File 34:SciSearch(R) Cited Ref Sci
(c) 2002 Inst for Sci Info. All rts. reserv.

06089708 Genuine Article#: XU625 Number of References: 43
Title: Human prostate tumor angiogenesis in nude mice: Metalloprotease and plasminogen activator activities during tumor growth and neovascularization of subcutaneously injected Matrigel impregnated with human prostate tumor cells (ABSTRACT AVAILABLE)
Author(s): Wilson MJ (REPRINT) ; Sinha AA
Corporate Source: VET ADM MED CTR, RES SERV, 1 VET DR/MINNEAPOLIS//MN/55417 (REPRINT); VET ADM MED CTR, DEPT LAB MED & PATHOL/MINNEAPOLIS//MN/55417; VET ADM MED CTR, DEPT UROL SURG/MINNEAPOLIS//MN/55417; VET ADM MED CTR, DEPT GENET & CELL BIOL/MINNEAPOLIS//MN/55417; UNIV MINNESOTA, CTR CANC/MINNEAPOLIS//MN/
Journal: ANATOMICAL RECORD, 1997, V249, N1 (SEP), P63-73
ISSN: 0003-276X Publication date: 19970900
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012

Language: English Document Type: ARTICLE

Abstract: Background: A critical aspect for growth of solid tumors is the development of a blood supply. Our objective was to establish a model for the study of angiogenesis of human prostate tumors by examining the growth of microvessels into Matrigel containing human prostate tumor cells implanted subcutaneously in nude mice,

Methods: Human prostate tumor cell lines PC-3 and LNCaP were injected in Matrigel under the abdominal skin of nude mice and were harvested at 4, 8, and 14 days post-injection. The growth of tumor cells and blood vessels was examined histologically and by immunohistochemical localization of von Willibrand Factor VIII (vWF). Since plasminogen activators and matrix metalloproteases are associated with angiogenesis, the activities and molecular forms of these proteases were determined in Matrigel control and Matrigel-tumor cell subcutaneous implants,

Results: blood vessel formation in the Matrigel implants containing LNCaP and PC-3 cells was demonstrable at 8 days post-injection. However, the pattern of blood vessel formation by the two tumor cell lines was different; PC-3 tumors showed a more invasive phenotype and smaller diameter blood vessels, whereas LNCaP tumors grew as large cellular spheroids surrounded by large, dilated blood vessels. Many blood vessels of PC-3 tumors expressed vWF by day 14 of growth, whereas most blood vessels in LNCaP tumors were immunohistochemically negative for this antigen. Mouse skin blood vessels in the same PC-3 and LNCaP tumor histological sections were positive for vWF.

Matrigel contained both plasminogen activator and metalloprotease

activities, The plasminogen activator activity in Matrigel control implants was totally inhibited by 4 days post-injection, indicating the presence of an inhibitor provided by the host mouse, LNCaP tumor cells **injected** did not have appreciable **plasminogen activator** activity, nor did LNCaP tumors develop plasminogen activator activity with tumor growth postinjection, PC-3 cells did have plasminogen activator activities, which were partially negated after subcutaneous injection (4 days), but then increased again by 8 days post-injection, This increase in **plasminogen activator** activity was due to urokinase (about 54 Ha) produced by the tumor and not by the mouse host (mouse urine urokinase about 44 kDa). Matrigel alone demonstrated gelatinase B (about 95 kDa) activity in zymograms, and gained considerable gelatinase A (about 70 and 74 kDa) activity after subcutaneous implantation. No metalloprotease activity from the tumor cells could be distinguished over that contributed by the mouse host cells in the Matrigel. Matrigel also contains caseinolytic activities of approximately 56, 80, 85, and 89 kDa. After subcutaneous injection of Matrigel, the 89 kDa form increases considerably in activity and the others are diminished. This pattern is also observed in LNCaP and PC-3 tumors post-injection, except the PC-3 tumors demonstrate increased 56 kDa activity.

Conclusion: The subcutaneous growth of LNCaP and PC-3 prostate tumor cells in Matrigel in nude mice can be used to study tumor-induced angiogenesis. However, the organization of LNCaP and PC-3 tumor growth and the pattern of microvessels associated with each tumor are different in this system, implying that each tumor has unique influences on the pattern of microvessel development. The mode of action by which this is brought about is not known, but may be due to specific factors produced/released by the tumor cells. (C) 1997 Wiley-Liss, Inc.*

...Abstract: injection, indicating the presence of an inhibitor provided by the host mouse, LNCaP tumor cells **injected** did not have appreciable **plasminogen activator** activity, nor did LNCaP tumors develop plasminogen activator activity with tumor growth postinjection, PC-3...

...partially negated after subcutaneous injection (4 days), but then increased again by 8 days post-injection, This increase in **plasminogen activator** activity was due to urokinase (about 54 Ha) produced by the tumor and not by...

5/3,K,AB/5 (Item 3 from file: 34)
 DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05356880 Genuine Article#: VT378 Number of References: 34
 Title: RETINAL CONTROL ON THE AXIAL LENGTH MEDIATED BY TRANSFORMING GROWTH-FACTOR-BETA IN CHICK EYE (Abstract Available)
 Author(s): HONDA S; FUJII S; SEKIYA Y; YAMAMOTO M
 Corporate Source: KOBE UNIV,SCH MED,DEPT OPHTHALMOL,CHUO KU,KUSUNOKI CHO 7-5-2/KOBE/HYOGO 650/JAPAN/
 Journal: INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, 1996, V37, N12 (NOV), P2519-2526
 ISSN: 0146-0404
 Language: ENGLISH Document Type: ARTICLE
 Abstract: Purpose. To clarify retinal control on scleral growth in form-deprivation myopia (FDM) in the chick, the authors studied change in transforming growth factor-beta (TGF-beta) in the form-deprived eye and the effect of this growth factor on scleral cell proliferation and axial length.

Methods. Change in TGF-beta in FDM in the chick Tvas measured by

reverse transcriptase polymerase chain reaction (RT-PCR), immunoblot, and immunohistochemistry. The effect of TGF-beta on [H-3] thymidine uptake of scleral chondrocytes was determined by organ culture. Urokinase plasminogen activator (uPA) and **plasminogen activator inhibitor-1 (PAI-1)** were **administered** to determine the effect of TGF-beta activation on the axial length in normal and FDM eyes.

Results. The content of TGF-beta messenger RNA (mRNA) and the active form of TGF-beta protein were reduced in FDM eyes compared with the control specimen. Reduced immunoreactivity of TGF-beta in FDM eyes was found in the photoreceptor layer. The TGF-beta inhibited [H-3] thymidine uptake into scleral chondrocytes. In the nondeprived eyes, the vitreous chamber depth and axial length were reduced after uPA treatment, whereas PAI-1 increased them. In the form-deprived eyes, uPA inhibited vitreous depth and axial length elongation, but PAI-1 had no effect.

Conclusions. The authors' results suggest that TGF-beta mediates retinal control of ocular growth. Axial elongation in FDM probably is correlated with the reduction of TGF-beta in the retina, retinal pigment epithelium, and choroid. The uPA and PAI-I treatment controls the activation of TGF-beta and affects axial length.

...Abstract: thymidine uptake of scleral chondrocytes was determined by organ culture. Urokinase plasminogen activator (uPA) and **plasminogen activator inhibitor-1 (PAI-1)** were **administered** to determine the effect of TGF-beta activation on the axial length in normal and...

...Research Fronts: 003 (TUMOR ANGIOGENESIS; INHIBITION OF VASCULAR ENDOTHELIAL GROWTH-FACTOR INDUCED CELL-GROWTH; STAGE-II BREAST-CANCER)

5/3,K,AB/6 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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1/16/01

03912642 Genuine Article#: QQ928 Number of References: 27
Title: STUDIES OF POSSIBLE MECHANISMS FOR THE EFFECT OF UROKINASE THERAPY IN SMALL-CELL CARCINOMA OF THE LUNG (Abstract Available)

Author(s): MEEHAN KR; ZACHARSKI LR; MAURER LH; HOWELL AL; MEMOLI VA; ROUSSEAU SM; HUNT JA; HENKIN J

Corporate Source: VET ADM MED CTR/WHITE RIVER JCT//VT/05009; VET ADM MED CTR/WHITE RIVER JCT//VT/05009; REG OFF CTR/WHITE RIVER JCT//VT/00000; DARTMOUTH COLL,SCH MED,DEPT MED,HEMATOL ONCOL SECT/LEBANON//NH/00000; DARTMOUTH COLL,SCH MED,DEPT PATHOL/LEBANON//NH/00000; ABBOTT LABS/ABBOTT PK//IL/60064

Journal: BLOOD COAGULATION & FIBRINOLYSIS, 1995, V6, N2 (APR), P105-112
ISSN: 0957-5235

Language: ENGLISH Document Type: ARTICLE

Abstract: Urokinase-type **plasminogen activator** has been **administered** by other investigators to patients with small cell carcinoma of the lung (SCCL) in an attempt to induce lysis of fibrin that is known to exist in the connective tissue stroma of this tumour type and that may support tumour growth. To study the fate of infused urokinase in this disease, a biopsy of a scalp metastasis was obtained from a patient with SCCL (entered on a phase I clinical trial of urokinase plus combination chemotherapy) immediately following urokinase infusion during the fourth course of therapy at a time when this tumour mass had decreased to approximately 25% of its original size. Immunohistochemical procedures revealed abundant stromal fibrin in accord with previous observations from this laboratory. By contrast, urokinase, that is not a feature of small cell tumour cells, was

present on the tumour cells in this specimen. Urokinase infusion was associated with a rapid increase in the amount of this enzyme associated with isolated peripheral blood monocytes. These results are consistent with uptake of infused urokinase onto monocytes and possibly tumour cells. It is postulated that substantial tumour fibrinolysis may not accompany such therapy and that urokinase, or its amino terminal fragment that bears the growth factor domain of this molecule, may bind to and alter the growth of the tumour cells.

Abstract: Urokinase-type **plasminogen activator** has been administered by other investigators to patients with small cell carcinoma of the lung (SCCL) in an...
...Identifiers--COAGULATION FIBRINOLYSIS; PLASMINOGEN-ACTIVATOR; GAMMA-INTERFERON; INDUCTION; **CANCER**; DIFFERENTIATION; EXPRESSION; LEUKEMIA; DOMAIN; LINE

5/3,K,AB/7 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2002 Inst for Sci Info. All rts. reserv.

03311349 Genuine Article#: NV078 Number of References: 33
Title: PREVENTION OF DELAYED ISCHEMIC DEFICITS AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE BY INTRATHECAL BOLUS **INJECTION** OF TISSUE-**PLASMINOGEN ACTIVATOR** (RTPA) - A PROSPECTIVE-STUDY (Abstract Available)
Author(s): SEIFERT V; STOLKE D; ZIMMERMANN M; FELDGES A
Corporate Source: UNIV ESSEN GESAMTHSCH,NEUROSURG CLIN,HUFELANDSTR 55/D-45122 ESSEN//GERMANY/
Journal: ACTA NEUROCHIRURGICA, 1994, V128, N1-4, P137-143
ISSN: 0001-6268
Language: ENGLISH Document Type: ARTICLE

Abstract: Among a series of 224 patients with aneurysmal subarachnoid haemorrhage (SAH) admitted over a period of three years, 52 patients were prospectively treated with intrathecal tissue plasminogen activator (rTPA). All of these patients were admitted and operated on within 72 h after SAH. SAH was confirmed by CT scan and the volume of blood accumulated in the basal cisterns was graded according to Fisher's scale. All patients had a SAH according to Fisher's grade III, as a prerequisite for inclusion into the study. In 21 patients additional intraventricular bleeding was detectable on CT scan. The diagnosis of a single intracerebral aneurysm as the bleeding source was established by pan-angiography, which also excluded additional cerebro-vascular malformations.

The control group consisted of 68 patients, which were also treated within 72 h after SAH. Age and sex distribution as well as the clinical patterns were comparable to the rTPA group.

In all patients the aneurysm was clipped using standard microsurgical techniques. After the aneurysm had been excluded from the parent vessel, 10 mg of rTPA, dissolved in 10 ml of its solution fluid, were slowly instilled into the basal cisterns in the treatment group. In patients with additional severe intraventricular bleeding, 5-10 mg of rTPA were injected into the ventricles via an intraventricular catheter at the end of the operation. Apart from the intrathecal application of the thrombolytic substance, the surgical protocol was identical in the patients of the control group.

During the postoperative period, the patients in both groups were examined neurologically and by transcranial Doppler on a daily basis. CT scans were performed on days 1, 2, 5, 10 postoperatively and immediately prior to discharge. Final clinical grading for this study was performed three months after surgery and the patients were graded

according to the Glasgow Outcome Scale. The occurrence of clinical signs of delayed ischaemic deficits (DID), attributable to the occurrence of cerebral vasospasm, was the only defined endpoint of the study. Radical blood clot removal, verified by serial CT scans was achieved in all patients treated using the intrathecal thrombolytic agent.

Overall results in the rTPA group at three months postsurgery were as follows: 39 patients (75%) were in grade I, 7 in grade II (13.5%), and 6 patients (11.5%) were in grade III GOS. Delayed ischaemic deficits, attributable to the occurrence of vasospasm were apparent in 4 patients (8%), in whom clinical symptoms were moderate in two patients and severe in another two. Three patients responded well to moderate hypertensive-hypervolaemic treatment resulting in an increase of their systolic arterial pressure up to 160 mm Hg. In none of these three patients cerebral infarction and/or permanent neurological deficits developed. In one patient with spasmogenic infarction of the middle cerebral artery territory in complete hemiparesis persisted. The overall results in the control group were as follows: 44 patients (64%) were in grade I GOS postoperatively, 6 in grade II (9%), 14 in grade III (21%), 1 in grade IV (1.5%), and three patients (4%) had died. DID attributable to the development of vasospasm developed in 16 patients (23.5%). DID were transient in 9 patients (13%) resolving completely after induction of hypertensive and hypervolaemic therapy. In four patients (6%) neurological deficits persisted despite vigorous treatment, and 3 patients (4%) died from spasmogenic cerebral infarction.

From the results of this first prospective study of a single bolus injection of rTPA in patients with aneurysm rupture, it is concluded, that intrathecal thrombolysis is an effective and safe method for removal of intracisternal blood accumulations after SAH resulting in a significant reduction of symptomatic vasospasm and DID. With regard to the radicality of blood clot removal achievable by the use of rTPA it is furthermore concluded, that conversion of a SAH according to Fisher grade III into a SAH of Fisher grade II is sufficient for significant reduction of the incidence of posthaemorrhagic DID, avoiding the necessity of complete pharmacological blood clot evacuation and the use of higher concentrations of rTPA or continuous irrigation of the subarachnoid space.

Title: PREVENTION OF DELAYED ISCHEMIC DEFICITS AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE BY INTRATHECAL BOLUS INJECTION OF TISSUE-PLASMINOGEN ACTIVATOR (RTPA) - A PROSPECTIVE-STUDY

...Research Fronts: PLASMINOGEN-ACTIVATOR)

92-1368 001 (TISSUE-TYPE PLASMINOGEN-ACTIVATOR; RECOMBINANT T-PA/U-PA CHIMERA; **CANCER** CELL UROKINASE RECEPTOR (UPAR))

5/3,K,AB/8 (Item 1 from file: 340)
DIALOG(R) File 340:CLAIMS(R)/US Patent
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Dialog Acc No: 3491420 IFI Acc No: 0113623
Document Type: C

USE OF AMILORIDE FOR TREATING **CANCER**; SYNERGISTIC MIXTURE WITH HYDROCHLOROTHIAZIDE

Inventors: Evans Douglas McCullough (US); Sloan-Stakleff Kimberly Denise (US)

Assignee: Unassigned Or Assigned To Individual Assignee Code: 68000

Publication (No,Date), Applic (No,Date)

US 6214824 20010410 US 99370643 19990806

Publication Kind:

Calculated Expiration: 20180916

Cont.-in-part Pub(No),Applic(No,Date): ABANDONED

US

98154345 19980916

Priority Applic(No,Date): US 99370643 19990806; US 98154345 19980916

Abstract:

Use of the proprietary drug amiloride for the treatment of **cancer** types that depend on an enzymatic cascade triggered by the activation of plasminogen to plasmin by the specific activating enzyme Urokinase Plasminogen Activator (uPA). Administration of amiloride inhibits the action of uPA, inhibits the ability of the **cancer** cell to attract new blood supply, blocks the Na⁺/H⁺ transporter, and inhibits ornithine decarboxylase necessary for DNA synthesis. Further, in combination with amiloride, a different step in the enzymatic cascade is targeted by a secondary agent, Batimistat, for example, which is a metalloprotease inhibitor. Additionally, the use of hydrochlorothiazide promotes excretion of potassium.

USE OF AMILORIDE FOR TREATING **CANCER**;

Abstract:

Use of the proprietary drug amiloride for the treatment of **cancer** types that depend on an enzymatic cascade triggered by the activation of plasminogen to plasmin...

...Activator (uPA). Administration of amiloride inhibits the action of uPA, inhibits the ability of the **cancer** cell to attract new blood supply, blocks the Na⁺/H⁺ transporter, and inhibits ornithine decarboxylase...

Exemplary Claim:

D R A W I N G

1. A method for treating a host having **cancer** cells derived from epithelial cells due to an enzymatic cascade triggered by the activation of plasminogen to plasmin by the specific activation of Urokinase Plasminogen Activator (uPA) comprising the steps of:
administering to the host an amount of amiloride sufficient to adversely affect the action of the uPA and thereby suppress invasion and spread of **cancer** cells in the host; and, administering a secondary agent to the host in combination with...

...in an amount effective to provide a synergistic effect on the invasion and spread of **cancer** cells in combination with the amiloride.

Non-exemplary Claims:

...4. A method for treating a host having **cancer** cells derived from epithelial cells due to an enzymatic cascade triggered by the activation of plasminogen to plasmin by the specific activation of Urokinase Plasminogen Activator (uPA) comprising the steps of:
administering to the host a combination of amiloride in the range of 0.3 mg/kg...

5/3,K,AB/9 (Item 2 from file: 340)

DIALOG(R) File 340:CLAIMS(R)/US Patent

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Dialog Acc No: 2757696 IFI Acc No: 9622399

Document Type: C

PHOSPHOROTHIOATE INHIBITORS OF METASTATIC BREAST **CANCER**; ANTITUMOR OR ANTICANCER AGENTS

Inventors: Iversen Patrick L (US); Scholar Eric M (US)

Assignee: Nebraska, University of Assignee Code: 58949

Publication (No,Date), Applic (No,Date)

US 5552390 19960903 US 93164200 19931209

Publication Kind: A

Calculated Expiration: 20131209
Priority Applic(No,Date): US 93164200 19931209

Abstract:

A method of inhibiting tumor invasion and metastasis of **cancer** cells using antisense oligonucleotides is disclosed. Phosphorothioate oligos were developed which are complementary to proteolytic enzymes such as urokinase plasminogen activator which are associated with invasion. In vitro and in vivo experiments with these oligos demonstrated highly significant reduction in tumor invasion and metastasis of mammary carcinoma cells.

PHOSPHOROTHIOATE INHIBITORS OF METASTATIC BREAST **CANCER**;

Abstract:

A method of inhibiting tumor invasion and metastasis of **cancer** cells using antisense oligonucleotides is disclosed. Phosphorothioate oligos were developed which are complementary to proteolytic...

Non-exemplary Claims:

...tumor cells in a mouse, said tumor cells exhibiting increased synthesis or secretion of urokinase **plasminogen activator**, comprising:
administering to said mouse an oligonucleotide selected from the group consisting of SEQ ID NO: 3...

...22. The method of claim 2 wherein said **cancer** cells are those of mammary carcinoma...

?

? ds

Set	Items	Description
S1	0	(ADMINISTER? OR INJECT?) (5N) (PLASMINOGENE(W)ACTIVATOR)
S2	703	(ADMINISTER? OR INJECT?) (5N) (PLASMINOGEN(W)ACTIVATOR)
S3	1035736	CANCER
S4	11	S2 AND S3
S5	9	RD (unique items)

? s captopril

S6	28131	CAPTOPRIL
----	-------	-----------

? s s2 and s6

	703	S2
	28131	S6
S7	0	S2 AND S6

? s sulfhydryl

S8	36512	SULFHYDRYL
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? s s2 and s8

	703	S2
	36512	S8
S9	0	S2 AND S8

?

? ds

Set	Items	Description
S1	880	(ADMINISTER? OR INJECT?) (5N) PLASMINOGEN
S2	52221	ANGIOGEN?
S3	14	S1 AND S2
S4	8	RD (unique items)

? s plasminogen

S5 80704 PLASMINOGEN
? s administer? or inject?

455161 ADMINISTER?
885444 INJECT?
S6 1261487 ADMINISTER? OR INJECT?
? s kringle or inhibitor??

2641 KRINGLE
1328379 INHIBITOR??
S7 1330363 KRINGLE OR INHIBITOR??
? s s5 and s6

80704 S5
1261487 S6
S8 6074 S5 AND S6
? s s8 not s7

6074 S8
1330363 S7
S9 3937 S8 NOT S7
? s s9 and s2

3937 S9
52221 S2
S10 54 S9 AND S2
? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...examined 50 records (50)
...completed examining records
S11 43 RD (unique items)
? s plasminogen(5n) fragment??

80704 PLASMINOGEN
474739 FRAGMENT??
S12 1608 PLASMINOGEN(5N) FRAGMENT??
? s s11 not s12

43 S11
1608 S12
S13 37 S11 NOT S12
? s activator

S14 152453 ACTIVATOR
? s s13 not s14

37 S13
152453 S14
S15 0 S13 NOT S14
?

S16 136 PLASMIN(5N) (ADMINISTER? OR INJECT?)
? ds

Set	Items	Description
S1	880	(ADMINISTER? OR INJECT?) (5N) PLASMINOGEN
S2	52221	ANGIOGEN?
S3	14	S1 AND S2
S4	8	RD (unique items)
S5	80704	PLASMINOGEN
S6	1261487	ADMINISTER? OR INJECT?
S7	1330363	KRINGLE OR INHIBITOR??
S8	6074	S5 AND S6
S9	3937	S8 NOT S7
S10	54	S9 AND S2
S11	43	RD (unique items)
S12	1608	PLASMINOGEN(5N) FRAGMENT??
S13	37	S11 NOT S12
S14	152453	ACTIVATOR
S15	0	S13 NOT S14
S16	136	PLASMIN(5N) (ADMINISTER? OR INJECT?)

? s s16 and s2

136 S16
52221 S2
S17 3 S16 AND S2
? rd

>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.

...completed examining records

S18 1 RD (unique items)
? t s18/3,k,ab/1

18/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10322326 99030426 PMID: 9813061

Macrophage formation of angiostatin during inflammation. A byproduct of the activation of plasminogen.

Falcone DJ; Khan KM; Layne T; Fernandes L

Department of Pathology, Cornell Medical College, New York, New York 10021, USA. dfalcone@mail.med.cornell.edu

Journal of biological chemistry (UNITED STATES) Nov 20 1998, 273 (47)

p31480-5, ISSN 0021-9258 Journal Code: HIV

Contract/Grant No.: R01-HL40819, HL, NHLBI; T32-HL07423-18, HL, NHLBI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Angiostatin is a potent inhibitor of tumor angiogenesis and the growth of metastatic foci. Recent studies have indicated that neoplastic cells can generate angiostatin directly or in cooperation with tumor-associated macrophages. In studies reported here, we determined whether angiostatin is generated in mice under non-neoplastic settings. Utilizing murine RAW264.7 macrophages and thioglycollate-elicited peritoneal macrophages, we demonstrate that angiostatin-like fragments are generated as a byproduct of the proteolytic regulation of membrane-bound plasmin. Plasmin proteolysis and subsequent loss in membrane-bound plasmin activity requires active plasmin but was unaffected by inhibitors of metalloproteinases. Lysine binding fragments of plasmin, isolated from macrophage-conditioned media utilizing affinity chromatography, appeared as a major (48 kDa) and two minor bands (42 and 50 kDa) in SDS-polyacrylamide

gel electrophoresis and were immunoreactive with anti-kringle 1-3 IgG. Each peptide begins with Lys77 and contains the entire sequence of angiostatin. The affinity isolated plasmin fragments inhibited bFGF-induced endothelial cell proliferation. Lavage fluid recovered from the peritoneal cavities of mice previously **injected** with thioglycollate contained angiostatin-like **plasmin** fragments similar to those generated in vitro. This is the first demonstration that angiostatin-like plasmin fragments are generated in a non-neoplastic inflammatory setting. Thus, in addition to regulating pericellular plasmin activity, proteolysis of plasmin generates inactive kringle-containing fragments expressing angiostatic properties.

Angiostatin is a potent inhibitor of tumor **angiogenesis** and the growth of metastatic foci. Recent studies have indicated that neoplastic cells can generate...

...bFGF-induced endothelial cell proliferation. Lavage fluid recovered from the peritoneal cavities of mice previously **injected** with thioglycollate contained angiostatin-like **plasmin** fragments similar to those generated in vitro. This is the first demonstration that angiostatin-like...
?

? s plasminogen

S1 80704 PLASMINOGEN
? s administer? or inject?

455161 ADMINISTER?
885444 INJECT?
S2 1261487 ADMINISTER? OR INJECT?
? s s1 and s2

80704 S1
1261487 S2
S3 6074 S1 AND S2
? s angiogen?

S4 52221 ANGIOGEN?
? s s3 and s4

6074 S3
52221 S4
S5 192 S3 AND S4
? t s5/3,k,ab/1-10

5/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

11796492 21485293 PMID: 11599799

Inhibition of endothelial cell proliferation and tumor-induced **angiogenesis** by pentoxifylline.

Gude RP; Binda MM; Boquete AL; Bonfil RD

Chemotherapy & Stem Cell Biology Division, Cancer Research Institute, Mumbai, India.

Journal of cancer research and clinical oncology (Germany) Oct 2001, 127 (10) p625-30, ISSN 0171-5216 Journal Code: HL5

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

PURPOSE: In this study we investigated the effect of pentoxifylline (PTX) on tumor-induced neovascularization as well as on different steps involved in the **angiogenic** process. METHODS: To assess **angiogenesis** inhibition. we **injected** intradermally (i.d.) 10 B16-F10 melanoma cells into C57BL/6J mice which were subsequently intraperitoneally (i.p.) inoculated with PTX or saline. On day 7 the number of blood vessels converging to the remnant of **injected** material was counted and the volumes of incipient tumors were calculated in each case. In vitro growth inhibition by PTX was evaluated in two different cell lines of endothelial origin and in human umbilical vein endothelial cells. Motility assays, as well as zymographic assays carried out to analyze gelatinolytic metalloproteinases and urokinase-type **plasminogen** activator, were performed in one of the endothelial cell lines. RESULTS: A significant inhibition of tumor-induced **angiogenesis** was observed in C57Bl/6 mice i.p. inoculated with PTX, that paralleled reduced incipient tumor volumes. The endothelial cells derived from different sources were inhibited in a dose-response manner by PTX in vitro. Non-cytotoxic PTX concentrations assayed in one of the endothelial cell lines did not inhibit its in vitro cell motility nor its gelatinase secretion, but its low molecular weight urokinase-type **plasminogen** activator expression. CONCLUSIONS: Our findings suggest that the inhibitory effect of PTX on tumor **angiogenesis** is related to antiproliferative action on endothelial cells, as well as to down regulation of u-PA secreted by them.

Inhibition of endothelial cell proliferation and tumor-induced

angiogenesis by pentoxifylline.

...pentoxifylline (PTX) on tumor-induced neovascularization as well as on different steps involved in the **angiogenic** process. METHODS: To assess **angiogenesis** inhibition. we **injected** intradermally (i.d.) 10 B16-F10 melanoma cells into C57BL/6J mice which were subsequently

... or saline. On day 7 the number of blood vessels converging to the remnant of **injected** material was counted and the volumes of incipient tumors were calculated in each case. In...

... assays, as well as zymographic assays carried out to analyze gelatinolytic metalloproteinases and urokinase-type **plasminogen** activator, were performed in one of the endothelial cell lines. RESULTS: A significant inhibition of tumor-induced **angiogenesis** was observed in C57BL/6 mice i.p. inoculated with PTX, that paralleled reduced incipient...

... in vitro cell motility nor its gelatinase secretion, but its low molecular weight urokinase-type **plasminogen** activator expression. CONCLUSIONS: Our findings suggest that the inhibitory effect of PTX on tumor **angiogenesis** is related to antiproliferative action on endothelial cells, as well as to down regulation of...

Descriptors: **Angiogenesis** Inhibitors--therapeutic use--TU; *Endothelium, Vascular--pathology--PA; *Melanoma, Experimental --drug therapy--DT; *Pentoxifylline--therapeutic...

Chemical Name: **Angiogenesis** Inhibitors; Pentoxifylline

5/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

11710234 21439149 PMID: 11555612

Soluble type II transforming growth factor-beta (TGF-beta) receptor inhibits TGF-beta signaling in COLO-357 pancreatic cancer cells in vitro and attenuates tumor formation.

Rowland-Goldsmith MA; Maruyama H; Kusama T; Ralli S; Korc M

Department of Medicine, University of California, Irvine, 92697, USA.

Clinical cancer research (United States) Sep 2001, 7 (9) p2931-40,

ISSN 1078-0432 Journal Code: C2H

Contract/Grant No.: CA-75059, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Human pancreatic ductal adenocarcinomas overexpress transforming growth factor-betas (TGF-betas). This overexpression has been correlated with decreased patient survival. TGF-betas bind to a type II TGF-beta receptor (TbetaRII) dimer, which heterotetramerizes with a type I TGF-beta receptor (TbetaRI) dimer, thereby activating downstream signaling. PURPOSE AND EXPERIMENTAL DESIGN: To determine whether blocking TGF-beta actions would suppress pancreatic cancer cell growth in vivo, we expressed a soluble TbetaRII, encoding amino acids 1-159 of the extracellular domain in COLO-357 human pancreatic cancer cells. This cell line expresses all of the three mammalian TGF-beta isoforms and is growth inhibited by TGF-beta in vitro. RESULTS: COLO-357 clones expressing soluble TbetaRII were no longer growth inhibited by exogenous TGF-beta and exhibited a marked decrease in their invasive capacity in vitro. When **injected** s.c. into athymic mice, these clones exhibited attenuated growth rates and **angiogenesis** and decreased levels of **plasminogen** activator inhibitor-1 mRNA as compared with tumors formed by sham-transfected cells. CONCLUSIONS: These results indicate that endogenous TGF-betas can confer a growth advantage in vivo to a pancreatic cancer cell line that is growth inhibited in vitro and suggest that a soluble receptor approach can be used to block these tumorigenic effects of TGF-betas.

... exogenous TGF-beta1 and exhibited a marked decrease in their invasive

capacity in vitro. When **injected** s.c. into athymic mice, these clones exhibited attenuated growth rates and **angiogenesis** and decreased levels of **plasminogen** activator inhibitor-1 mRNA as compared with tumors formed by sham-transfected cells. CONCLUSIONS: These...

5/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

11598415 21370053 PMID: 11477374

Metabolism of rabbit angiostatin glycoforms I and II in rabbits: angiostatin-I leaves the intravascular space faster and appears to have greater anti-**angiogenic** activity than angiostatin-II.

Hatton MW; Day S; Southward SM; Dereske M; Ross B; Seidlitz E; Singh G; Richardson M

Department of Pathology and Molecular Medicine, McMaster University Health Sciences Centre, and the Hamilton Regional Cancer Centre, Ontario, Canada.

Journal of laboratory and clinical medicine (United States) Aug 2001, 138 (2) p83-93, ISSN 0022-2143 Journal Code: IVR

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Plasminogen (PLG) exists in the circulation as two glycoforms, I and II. Angiostatin (AST) is a polypeptide that has been cleaved from the kringle region of PLG and has strong anti-**angiogenic** properties. AST-I and AST-II, which consisted only of kringles 1 through 3, were prepared by the action of urokinase on purified rabbit PLG-I and PLG-II, respectively, in the presence of N-acetyl cysteine, followed by affinity chromatography on lysine-Sepharose. Purified AST-I and AST-II were tested for functional activity with a chick chorioallantoic membrane (CAM) model; when similar amounts were applied to a 6-day CAM, AST-I was substantially more effective than AST-II in decreasing vascular supply to the CAM over a 72-hour period; this activity correlated with a loss of capillaries, probably through apoptosis of endothelial cells. Radiolabeled AST-I and AST-II (iodine 125 and iodine 131) were co-**injected** intravenously into healthy rabbits to determine their clearances from plasma measured over 3 days. Over a dose range of 0.08 to 2.7 microg/kg, the fractional catabolic rate within the intravascular space (j(3)) indicated that AST-I was cleared 3-fold to 4-fold more rapidly than AST-II (P < .001). The catabolic half-life of AST-I (2.01 +/- 0.19 days) was significantly less than that of AST-II (2.62 +/- 0.20 days). The faster clearance of AST-I from the intravascular space was matched by its more rapid passage than AST-II to the extravascular space of various organs over 60 minutes in vivo. This property of AST-I as compared with AST-II may partially explain its greater anti-**angiogenic** potential. From the plasma concentrations of PLG-I and PLG-II and their relative behaviors toward rabbit VX-2 lung tumors in vivo, we predict that substantially greater quantities of AST-II than AST-I may be released into the extravascular space of tumors.

... in rabbits: angiostatin-I leaves the intravascular space faster and appears to have greater anti-**angiogenic** activity than angiostatin-II.

Plasminogen (PLG) exists in the circulation as two glycoforms, I and II. Angiostatin (AST) is a polypeptide that has been cleaved from the kringle region of PLG and has strong anti-**angiogenic** properties. AST-I and AST-II, which consisted only of kringles 1 through 3, were...

... endothelial cells. Radiolabeled AST-I and AST-II (iodine 125 and iodine 131) were co-**injected** intravenously into healthy rabbits to determine their clearances from plasma measured over 3 days. Over...

... property of AST-I as compared with AST-II may partially explain its greater anti-**angiogenic** potential. From the plasma concentrations of PLG-I and PLG-II and their relative behaviors...

Descriptors: Neovascularization, Physiologic--drug effects--DE; *Peptide Fragments--pharmacokinetics--PK; *Plasminogen--pharmacokinetics--PK ...; Radioisotopes--diagnostic use--DU; Isomerism; Peptide Fragments--chemistry--CH; Peptide Fragments--isolation and purification--IP; Plasminogen--chemistry--CH; Plasminogen --isolation and purification--IP; Rabbits; Species Specificity; Tarsal Joint--metabolism--ME

Chemical Name: Iodine Radioisotopes; Peptide Fragments; angiostatin; Plasminogen

5/3,K,AB/4 (Item 4 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

11557760 21369814 PMID: 11477587

Mouse macrophage metalloelastase gene delivery by HVJ-cationic liposomes in experimental antiangiogenic gene therapy for murine CT-26 colon cancer.

Gorrrin-Rivas MJ; Arii S; Mori A; Kaneda Y; Imamura M

Department of Surgery and Surgical Basic Science, Graduate School of Medicine, Kyoto University, Kyoto, Japan. mjgorrrin2@yahoo.com

International journal of cancer. Journal international du cancer (United States) Sep 1 2001, 93 (5) p731-5, ISSN 0020-7136 Journal Code: GQU

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

We previously demonstrated that gene replacement of mouse macrophage metalloelastase (MME) into murine melanoma cells that grow rapidly and are MME deficient suppresses the primary tumor growth in vivo by halting **angiogenesis**. The aim of the present study was to evaluate the effectiveness of gene therapy against cancer using a cDNA-encoding MME gene. In a subcutaneous tumor model of CT-26 mouse colon cancer cells that are MME deficient, syngeneic mice repetitively treated with direct **injections** into the tumors of MME- hemagglutinating virus of Japan (HVJ), a type of HVJ-cationic liposome encapsulating a plasmid expressing MME, developed smaller tumors (210 +/- 47.2 mm(3) versus 925 +/- 156 mm(3) mean +/- SEM; p = 0.0004) with fewer microvessels (10.25 +/- 1.03 vs. 17.25 +/- 2.14; p = 0.03) than control mice. TUNEL staining revealed a significant increase of apoptotic cells in the MME-HVJ liposomes-treated tumors compared with control tumors. MME was effectively expressed in the s.c. tumors treated with MME-HVJ liposomes, inducing angiostatin generation in those tumors, as demonstrated by Western blot analysis. In conclusion, our study demonstrated that repeated in vivo transduction of the MME gene directly into the tumors using HVJ-cationic liposomes suppressed the tumor growth by an antiangiogenic mechanism, providing, then, a feasible strategy for gene therapy of cancer. Copyright 2001 Wiley-Liss, Inc.

...grow rapidly and are MME deficient suppresses the primary tumor growth in vivo by halting **angiogenesis**. The aim of the present study was to evaluate the effectiveness of gene therapy against...

... 26 mouse colon cancer cells that are MME deficient, syngeneic mice repetitively treated with direct **injections** into the tumors of MME- hemagglutinating virus of Japan (HVJ), a type of HVJ-cationic...

...; Neoplasms, Experimental--genetics--GE; Neoplasms, Experimental--therapy--TH; Paramyxovirus--chemistry--CH; Peptide Fragments--pharmacology--PD; Plasminogen--pharmacology--PD; Transfection; Tumor Cells, Cultured

Chemical Name: Antineoplastic Agents; Drug Carriers; Liposomes; Peptide Fragments; angiostatin; Plasminogen; Metalloendopeptidases; alveolar macrophage elastase

5/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

11529881 21240687 PMID: 11342643

Combined treatment of a murine breast cancer model with type 5 adenovirus vectors expressing murine angiostatin and IL-12: a role for combined anti-**angiogenesis** and immunotherapy.

Gyorffy S; Palmer K; Podor TJ; Hitt M; Gauldie J

Department of Pathology and Molecular Medicine, Centre for Gene Therapeutics, McMaster University, Hamilton, Ontario, Canada.

Journal of immunology (United States) May 15 2001, 166 (10) p6212-7, ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

In this study, we used intratumor delivery of adenoviral vectors to induce a selective anti-tumor response by combining the potent **angiogenesis** inhibitor murine angiostatin (adenovirus (Ad)-angiostatin) with the powerful immune simulator and angiostatic cytokine murine IL-12 (Ad-IL-12). In a murine model of breast carcinoma, intratumor **injection** of Ad-angiostatin delayed mean tumor growth, as compared with control virus with an initial regression of tumor growth, in 65% of treated animals. However, all treated animals eventually succumbed to the tumors. Mice **injected** with Ad-IL-12 alone responded with an initial regression in 20% of treated animals, with only 13% developing a total regression. Coinjection of the vectors resulted in 96% of the treated animals developing an initial regression, with 54% undergoing a total regression of the tumor. These mice were resistant to tumor rechallenge and developed a strong CTL response. Frozen tumor sections were stained for microvessel density using an Ab against murine CD31, an endothelial cell marker. Automated image analysis revealed the mean microvessel density following the administration of Ad-angiostatin and Ad-IL-12 alone or in combination was significantly reduced compared with the control-treated tumor. In summary, we have shown that a short-term course of antiangiogenic therapy combined with immunotherapy can effectively shrink a solid tumor and vaccinate the animal against rechallenge. The rationale for this therapy is to limit the tumor size by attacking the vasculature with angiostatin, thereby allowing IL-12 to mount a T cell-specific response against the tumor AG:

... type 5 adenovirus vectors expressing murine angiostatin and IL-12: a role for combined anti-**angiogenesis** and immunotherapy.

... delivery of adenoviral vectors to induce a selective anti-tumor response by combining the potent **angiogenesis** inhibitor murine angiostatin (adenovirus (Ad)-angiostatin) with the powerful immune simulator and angiostatic cytokine murine IL-12 (Ad-IL-12). In a murine model of breast carcinoma, intratumor **injection** of Ad-angiostatin delayed mean tumor growth, as compared with control virus with an initial ...

... in 65% of treated animals. However, all treated animals eventually succumbed to the tumors. Mice **injected** with Ad-IL-12 alone responded with an initial regression in 20% of treated animals...

...Descriptors: Immunotherapy, Active; *Interleukin-12--genetics--GE; *Mammary Neoplasms, Experimental--therapy--TH; *Peptide Fragments--genetics--GE; *Plasminogen--genetics--GE; Adenocarcinoma--blood supply--BS; Adenocarcinoma--genetics--GE; Adenocarcinoma--immunology--IM; Adenocarcinoma--therapy--TH; **Angiogenesis** Inhibitors--administration and dosage--AD; Antigens, CD31--immunology--IM; Antigens, Polyomavirus Transforming--biosynthesis--BI; Antigens...

...Genetic Vectors--administration and dosage--AD; Immune Sera--analysis--AN; Immunohistochemistry; Immunotherapy, Active--methods--MT; **Injections**, Intranasal; **Injections**, Subcutaneous; Interleukin-12--administration and dosage--AD; Interleukin-12--biosynthesis--BI; Mammary Neoplasms, Experimental--blood...

...Strains; Mice, Transgenic; Neoplasm Transplantation; Peptide Fragments
--administration and dosage--AD; Peptide Fragments--biosynthesis--BI;
Plasminogen--administration and dosage--AD; **Plasminogen**
--biosynthesis--BI; Staining and Labeling; Tumor Cells, Cultured
Chemical Name: **Angiogenesis** Inhibitors; Antigens, CD31; Antigens,
Polyomavirus Transforming; Antineoplastic Agents, Combined; Genetic Vectors
; Immune Sera; Interleukin-12; Peptide Fragments; angiostatin;
Plasminogen

5/3,K,AB/6 (Item 6 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

11427786 21333423 PMID: 11440369

Intravitreal **injection** of **plasminogen** kringle 5, an
endogenous **angiogenic** inhibitor, arrests retinal neovascularization
in rats.

Zhang D; Kaufman PL; Gao G; Saunders RA; Ma JX
Department of Ophthalmology, Medical University of South Carolina,
Charleston 29403, USA.

Diabetologia (Germany) Jun 2001, 44 (6) p757-65, ISSN 0012-186X
Journal Code: E93

Contract/Grant No.: EY12231, EY, NEI; EY12600, EY, NEI

Languages: ENGLISH

Document type: Journal Article

Record type: In Process

AIMS/HYPOTHESIS: **Plasminogen** kringle 5 is an endogenous
angiogenic inhibitor. The purpose of the present study was to explore
the potential application of kringle 5 in the treatment of retinal
neovascularization. METHODS: **Plasminogen** kringle 5 was expressed in
E. coli and affinity-purified. Its anti-**angiogenic** activity was
determined in cultured primary human capillary endothelial cells. Retinal
neovascularization was induced in newborn rats by exposure to hyperoxia and
then normoxia. Kringle 5 was intravitreally **injected** into the rat
model. Retinal neovascularization was visualized by fluorescein angiography
on flat-mounted retina and quantified by counting preretinal vascular
cells. RESULTS: **Plasminogen** kringle 5 inhibited primary endothelial
cells but not retinal neuronal cells, suggesting cell type-specific
inhibition. The oxygen-induced retinopathy rat model showed an
over-expression of vascular endothelial growth factor, preretinal
neovascularization and haemorrhage. Intravitreal **injection** of kringle
5 before the development of neovascularization resulted in fewer
neovascular tufts and pre-retinal vascular cells than in control rats with
PBS **injection** ($p < 0.01$). Moreover, **injection** of kringle 5
after the development of neovascularization inhibited the increase in the
preretinal vascular cells ($p < 0.05$). These results suggest that kringle 5
both prevents the development and arrests the progression of retinal
neovascularization. The **injection** of kringle 5 did not result in any
detectable inflammatory response in the retina or histological toxicity to
retina neurons and pre-existing vessels. CONCLUSION/INTERPRETATION: These
observations suggest that intravitreal delivery of **angiogenic**
inhibitors could have therapeutic benefits in neovascular diseases of the
retina.

Intravitreal **injection** of **plasminogen** kringle 5, an
endogenous **angiogenic** inhibitor, arrests retinal neovascularization
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AIMS/HYPOTHESIS: **Plasminogen** kringle 5 is an endogenous
angiogenic inhibitor. The purpose of the present study was to explore
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determined in cultured primary human capillary endothelial cells. Retinal

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...that kringle 5 both prevents the development and arrests the progression of retinal neovascularization. The **injection** of kringle 5 did not result in any detectable inflammatory response in the retina or...

... retina neurons and pre-existing vessels. CONCLUSION/INTERPRETATION: These observations suggest that intravitreal delivery of **angiogenic** inhibitors could have therapeutic benefits in neovascular diseases of the retina.

5/3,K,AB/7 (Item 7 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

11337027 21221190 PMID: 11320411

Recombinant angiostatin prevents retinal neovascularization in a murine proliferative retinopathy model.

Meneses PI; Hajjar KA; Berns KI; Duvoisin RM

Department of Microbiology, Weill Medical College of Cornell University, New York, NY, USA.

Gene therapy (England) Apr 2001, 8 (8) p646-8, ISSN 0969-7128

Journal Code: CCE

Contract/Grant No.: AI22251, AI, NIAID; EY09534, EY, NEI; EY13101, EY, NEI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Retinal neovascularization is central to the pathogenesis of proliferative diabetic retinopathy, the leading cause of blindness among the middle-aged population. Angiostatin, a proteolytic fragment of **plasminogen** is one of the most promising inhibitors of **angiogenesis** currently in clinical trials. Here we show that recombinant angiostatin can inhibit retinal neovascularization in a mouse model of proliferative retinopathy. Because proliferative diabetic retinopathy is a recurrent disease, effective therapy will need to be sustained. Recombinant adeno-associated viruses permit long-term expression of transfected genes; however, they can only accommodate a small insert sequence. Thus, we engineered and tested a shortened recombinant angiostatin derivative containing a signal sequence to permit secretion. Recombinant protein was purified from the medium of transfected HEK293 cells and **injected** subcutaneously into treated animals. The retinal vasculature was analyzed in retinal flat mounts and using immunohistochemically stained sections. Both methods demonstrate that this short, secreted form of angiostatin is effective in reducing the development of blood vessels in a nontumor environment and has therapeutic potential for neovascular retinopathies such as diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion and, possibly, age-related macular degeneration.

... the leading cause of blindness among the middle-aged population. Angiostatin, a proteolytic fragment of **plasminogen** is one of the most

promising inhibitors of **angiogenesis** currently in clinical trials. Here we show that recombinant angiostatin can inhibit retinal neovascularization in...

...to permit secretion. Recombinant protein was purified from the medium of transfected HEK293 cells and **injected** subcutaneously into treated animals. The retinal vasculature was analyzed in retinal flat mounts and using...

Descriptors: Diabetic Retinopathy--prevention and control--PC; *Peptide Fragments--therapeutic use--TU; ***Plasminogen**--therapeutic use--TU; *Retinal Neovascularization--prevention and control--PC
Chemical Name: Peptide Fragments; Recombinant Proteins; angiostatin; **Plasminogen**

5/3,K,AB/8 (Item 8 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

11266771 21205848 PMID: 11309307

Down-regulation of vascular endothelial growth factor by tissue inhibitor of metalloproteinase-2: effect on in vivo mammary tumor growth and **angiogenesis**.

Hajitou A; Sounni NE; Devy L; Grignet-Debrus C; Lewalle JM; Li H; Deroanne CF; Lu H; Colige A; Nusgens BV; Franken F; Maron A; Yeh P; Perricaudet M; Chang Y; Soria C; Calberg-Bacq CM; Foidart JM; Noel A

Laboratories of Tumor and Development Biology, University of Liege, Sart-Tilman, 4000 Liege, Belgium.

Cancer research (United States) Apr 15 2001, 61 (8) p3450-7, ISSN 0008-5472 Journal Code: CNF

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The tissue inhibitor of metalloproteinases-2 (TIMP-2) has at least two independent functions, i.e., regulation of matrix metalloproteinases and growth promoting activity. We investigated the effects of TIMP-2 overexpression, induced by retroviral mediated gene transfer, on the in vivo development of mammary tumors in syngeneic mice inoculated with EF43.fgf-4 cells. The EF43.fgf-4 cells established by stably infecting the normal mouse mammary EF43 cells with a retroviral expression vector for the fgf-4 oncogene, are highly tumorigenic and overproduce vascular endothelial growth factor (VEGF). Despite a promotion of the in vitro growth rate of EF43.fgf-4 cells overexpressing timp-2, the in vivo tumor growth was delayed. At day 17 post-cell **injection**, the volume of tumor derived from TIMP-2-overexpressing cells was reduced by 80% as compared with that obtained with control cells. Overexpression of TIMP-2 was associated with a down-regulation of VEGF expression in vitro and in vivo, a reduction of vessel size, density, and blood supply in the induced tumors. In addition, TIMP-2 completely inhibited the **angiogenic** activity of EF43.fgf-4 cell-conditioned medium in vitro using a rat aortic ring model. Our findings suggest that overexpression of TIMP-2 delays growth and **angiogenesis** of mammary carcinoma in vivo and that down-regulation of VEGF expression may play an important role in this TIMP-2-mediated antitumoral and antiangiogenic effects. Finally the in vivo delivery of TIMP-2, as assessed by i.v. **injection** of recombinant adenoviruses vectors, significantly reduced the growth of the EF43.fgf-4-induced tumors. This effect of TIMP-2 was shown to be equally comparable with that of angiostatin, a known potent inhibitor of **angiogenesis**.

... factor by tissue inhibitor of metalloproteinase-2: effect on in vivo mammary tumor growth and **angiogenesis**.

...overexpressing timp-2, the in vivo tumor growth was delayed. At day 17 post-cell **injection**, the volume of tumor derived from TIMP-2-overexpressing cells was reduced by 80% as...

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... antiangiogenic effects. Finally the in vivo delivery of TIMP-2, as assessed by i.v. **injection** of recombinant adenoviruses vectors, significantly reduced the growth of the EF43.fgf-4-induced tumors...

... was shown to be equally comparable with that of angiostatin, a known potent inhibitor of **angiogenesis**.

...; Pathologic--genetics--GE; Neovascularization, Pathologic
--metabolism--ME; Peptide Fragments--genetics--GE; Peptide Fragments
--physiology--PH; **Plasminogen**--genetics--GE; **Plasminogen**
--physiology--PH; Rats; Tissue Inhibitor-of Metalloproteinase-2
--biosynthesis--BI; Tissue Inhibitor-of Metalloproteinase-2...

...Chemical Name: growth factor-14; vascular permeability factor; Tissue Inhibitor-of Metalloproteinase-2; Fibroblast Growth Factor; angiostatin; **Plasminogen**

5/3,K,AB/9 (Item 9 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

11265063 21189159 PMID: 11292663

Influence of **plasminogen** activator inhibitor type 1 on choroidal neovascularization.

Lambert V; Munaut C; Noel A; Franken F; Bajou K; Gerard R; Carmeliet P; Defresne MP; Foidart JM; Rakic JM

Laboratory of Tumor and Development Biology, University of Liege, B-4000 Liege, Belgium. vincent.lambert@ulg.ac.be

FASEB journal (United States) Apr 2001, 15 (6) p1021-7, ISSN 0892-6638 Journal Code: FAS

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

High levels of the **plasminogen** activators, but also their inhibitor, **plasminogen** activator inhibitor 1 (PAI-1), have been documented in neovascularization of severe ocular pathologies such as diabetic retinopathy or age-related macular degeneration (AMD). AMD is the primary cause of irreversible photoreceptors loss, and current therapies are limited. PAI-1 has recently been shown to be essential for tumoral **angiogenesis**. We report here that deficient PAI-1 expression in mice prevented the development of subretinal choroidal **angiogenesis** induced by laser photocoagulation. When systemic and local PAI-1 expression was achieved by intravenous **injection** of a replication-defective adenoviral vector expressing human PAI-1 cDNA, the wild-type pattern of choroidal **angiogenesis** was restored. These observations demonstrate the proangiogenic activity of PAI-1 not only in tumoral models, but also in choroidal experimental neovascularization sharing similarities with human AMD. They identify therefore PAI-1 as a potential target for therapeutic ocular anti-**angiogenic** strategies.

Influence of **plasminogen** activator inhibitor type 1 on choroidal neovascularization.

High levels of the **plasminogen** activators, but also their inhibitor, **plasminogen** activator inhibitor 1 (PAI-1), have been documented in neovascularization of severe ocular pathologies such...

... current therapies are limited. PAI-1 has recently been shown to be essential for tumoral **angiogenesis**. We report here that deficient PAI-1 expression in mice prevented the development of subretinal choroidal

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... human AMD. They identify therefore PAI-1 as a potential target for therapeutic ocular anti-**angiogenic** strategies.

Descriptors: Choroidal Neovascularization--physiopathology--PP; *
Plasminogen Activator Inhibitor 1--physiology--PH; Adenoviridae
--genetics--GE; DNA, Complementary--genetics--GE; Genetic Vectors; Mice;
Mice, Inbred C57BL; Mice, Knockout; **Plasminogen** Activator Inhibitor 1
--genetics--GE; Transfection
Chemical Name: DNA, Complementary; Genetic Vectors; **Plasminogen**
Activator Inhibitor 1

5/3,K,AB/10 (Item 10 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

11203228 21175001 PMID: 11280788

Radiation therapy to a primary tumor accelerates metastatic growth in mice.

Camphausen K; Moses MA; Beecken WD; Khan MK; Folkman J; O'Reilly MS
Joint Center for Radiation Therapy, Harvard Medical School, Boston,
Massachusetts 02115, USA.

Cancer research (United States) Mar 1 2001, 61 (5) p2207-11, ISSN
0008-5472 Journal Code: CNF

Contract/Grant No.: P01 CA45548, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The surgical removal of a primary tumor can result in the rapid growth of metastases. The production of **angiogenesis** inhibitors by the primary tumor is one mechanism for the inhibition of metastatic tumor growth. The effect of curative radiotherapy to a primary tumor known to make an inhibitor of **angiogenesis** and the effects on distant metastases has not been studied. We here show that the eradication of a primary Lewis lung carcinoma (LLC-LM), which is known to generate angiostatin, is followed by the rapid growth of metastases that kill the animal within 18 days after the completion of radiation therapy. The right thighs of C57BL/6 mice (n = 25) were **injected** s.c. with 1×10^6 LLC-LM cells. Animals were randomized to one of five groups: no irradiation, 40 Gy in one fraction, 30 Gy in one fraction, 40 Gy in two 20 Gy fractions, or 50 Gy in five 10 Gy fractions. Tumors were clinically eradicated in each treatment group. All of the surviving animals became dyspneic and were killed within 14-18 days after the completion of radiation therapy. Examination of their lungs revealed >46 (range, 46-62) surface metastases in the treated animals compared with 5 (range, 2-8) in the untreated animals. The lung weights had increased from 0.2 g (range, 0.19-0.22 g) in the controls to 0.58 g (range 0.44-0.84) in the experimental animals. The most effective dose regimen was 10 Gy per fraction for five fractions, and serial experiments were conducted with this fractionation scheme. Complete response of the primary tumor was seen in 25 of 35 (71%) mice. The average weight of the lungs in the nonirradiated animals was 0.22 g (range, 0.19-0.24 g) and in the irradiated animals was 0.66 g (range, 0.61-0.70 g). The average number of surface metastases increased from five per lung (range, 2-13) in the control animals to 53 per lung (range, 46-62) in the irradiated animals. Both differences were statistically significant with $P < 0.001$. If the nontumor-bearing leg was irradiated or the animals were sham-irradiated, no difference in the number of surface metastases or lung weights was observed between the control group and the treated group. Urinary levels of matrix metalloproteinase 2, the enzyme responsible for angiostatin processing in

this tumor model, were measured and correlated with the viability and size of the primary tumor. Administration of recombinant angiostatin prevented the growth of the metastases after the treatment of the primary tumor. In this model, the use of radiation to eradicate a primary LLC-LM tumor results in the growth of previously dormant lung metastases and suggests that combining **angiogenesis** inhibitors with radiation therapy may control distant metastases.

... of a primary tumor can result in the rapid growth of metastases. The production of **angiogenesis** inhibitors by the primary tumor is one mechanism for the inhibition of metastatic tumor growth. The effect of curative radiotherapy to a primary tumor known to make an inhibitor of **angiogenesis** and the effects on distant metastases has not been studied. We here show that the...

...the completion of radiation therapy. The right thighs of C57BL/6 mice (n = 25) were **injected** s.c. with 1×10^6 LLC-LM cells. Animals were randomized to one...

...LM tumor results in the growth of previously dormant lung metastases and suggests that combining **angiogenesis** inhibitors with radiation therapy may control distant metastases.

; **Angiogenesis** Inhibitors--pharmacology--PD; Antineoplastic Agents --pharmacology--PD; Carcinoma, Lewis Lung--enzymology--EN; Carcinoma, Lewis Lung...

...C57BL; Neoplasm Transplantation; Peptide Fragments--biosynthesis--BI; Peptide Fragments--pharmacology--PD; Peptide Fragments--physiology--PH; **Plasminogen**--biosynthesis--BI; **Plasminogen**--pharmacology--PD; **Plasminogen**--physiology--PH; Radiotherapy--adverse effects--AE

Chemical Name: **Angiogenesis** Inhibitors; Antineoplastic Agents; Peptide Fragments; angiostatin; **Plasminogen**; Gelatinase A

?